Protective strategy shields primate ovaries from radiation-therapy-induced damage

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A strategy developed by Massachusetts General Hospital (MGH) researchers to shield the ovaries of female mammals from the damaging effects of radiation and chemotherapy has passed an important milestone. A collaborative study with investigators from Oregon Health and Sciences University (OHSU), published online in the journal Fertility and Sterility, reports that brief preexposure of the ovaries to an FDA-approved agent called FTY720 preserved the fertility of female rhesus monkeys exposed to potentially lethal doses of radiation. All of the treated animals have had successful pregancies and delivered healthy offspring.

"When we started working on this project in the mid-1990s, the only strategy available to preserve the fertility of cancer patients was collecting and freezing eggs or ovarian tissue for assisted reproduction, neither of which offered much in terms of successful pregnancies," explains Jonathan Tilly, PhD, director of the Vincent Center for Reproductive Biology in the MGH Department of Obstetrics and Gynecology, senior author of the Fertility and Sterility article. "Since then we have brought the concept of protecting the ovaries from damage caused by anticancer treatments all the way from an idea on paper, through a decade of mouse studies, to a proof of concept in living primates."

In 1997 Tilly and collaborators at the MGH and other research centers discovered that treatment with chemotherapy drugs led to the death of egg cells in mice through a process known as apoptosis – used naturally

by the body to delete unwanted or damaged cells – and also identified the specific cell-death pathway involved. A follow-up 2000 study from Tilly's group showed that blocking that pathway with a compound called sphingosine-1-phosphate (S1P) preserved the egg cells (oocytes) of mice exposed to radiation therapy, which activates the same cell-death pathway as chemotherapy; and that those oocytes could be fertilized. A third study from Tilly and colleagues at Memorial Sloan-Kettering Cancer Institute reported in 2002 that S1P-pretreated female mice that were mated two months after receiving radiotherapy successfully delivered litters of healthy offspring.

Testing this approach in primates presented several challenges, so before attempting a trial in monkeys, the researchers wanted to be sure that S1P would also protect human oocytes. Ovarian tissue from human patients was grafted into immunodeficient mice, and some of the animals were treated with S1P for an hour before the tissue was exposed to radiation. The experiment showed that the resting pool of follicles from which oocytes develop into mature eggs was protected in the S1P-treated animals but was largely depleted in the human grafts not protected with S1P.

Another potential obstacle to bringing this approach from mice to primates is the fact that rodent ovaries are enclosed in a membrane sac, confining any drug injected into the sac to the ovary. Primate ovaries are free of any such enclosure, presenting the risk that any protective agent applied to the ovary might escape and protect tumor cells as well. Fortunately, investigators at the Oregon National Primate Research Center based at OHSU had already developed an implantable miniature pump that could deliver a drug to the ovaries alone.

In the current study, the OHSU team, led by Mary Zelinski, PhD, conducted a series of experiments, the first of which confirmed that delivering S1P directly to the ovaries of rhesus monkeys provided the

same sort of protection from radiation effects seen in the earlier mouse studies. Since S1P is a rather unstable molecule that is broken down quickly, the researchers then tried using FTY720, a long-acting S1P-like agent with similar effects that also is approved for the treatment of multiple sclerosis. Treatment with FTY720, also called fingolimod, was even more successful than S1P in protecting monkey ovarian follicles from radiation-induced cell death.

In the final experiment, radiation was delivered directly to the ovaries of three female monkeys that had been pretreated with FTY720. A control group of three underwent a sham radiation treatment after receiving an inert infusion. Both groups resumed normal menstrual cycles, were successfully mated, and all have delivered offspring that appear normal and healthy. Two of the three radioprotected females have become pregnant a second time and delivered two more healthy offspring. Because female monkeys without normal ovarian function will not mate, there was no mating test of irradiation without FTY720 protection, since those animals would have complete ovarian destruction.

"This first generation of offspring born to FTY720-protected mothers have been assessed anatomically and behaviorally, as well as with the most sensitive assay we have for propagated genetic damage, and everything looks fine," says Tilly. "They are now about 2 years old and approaching sexual maturation, so we want to make sure they are reproductively normal and that the second-generation offspring will also be normal."

Tilly stresses, "The damage that anticancer treatments inflict on women's ovaries not only destroys their fertility, it also exposes them to the health risks of premature ovarian failure. The animals in this study have maintained ovarian function – they are still having normal menstrual cycles – several years after they were treated, which is critical. There are a handful of approaches out there that might give cancer patients a shot

at preserving fertility, but this is currently the only option on the table for preventing premature menopause."

The current study, Tilly adds, is also an illustration of the power of collaboration. "This work could not have been done without the vast experience in primate ovarian biology of Mary Zelinski and her team at OHSU. We brought the science developed from more than a decade of mouse studies and, by working together with Mary's team, successfully translated that work from mice to primates, enabling us now to say with confidence that this approach has a good chance of succeeding in human pateents." A professor of Obstetrics, Gynecology and Reproductive Biology at Harvard Medical School, Tilly hopes to next plan a clinical trial in human cancer patients, in collaboration with colleagues from the MGH Cancer Center.

Provided by Massachusetts General Hospital