Available drug may protect ovaries and fertility from damage by chemotherapies

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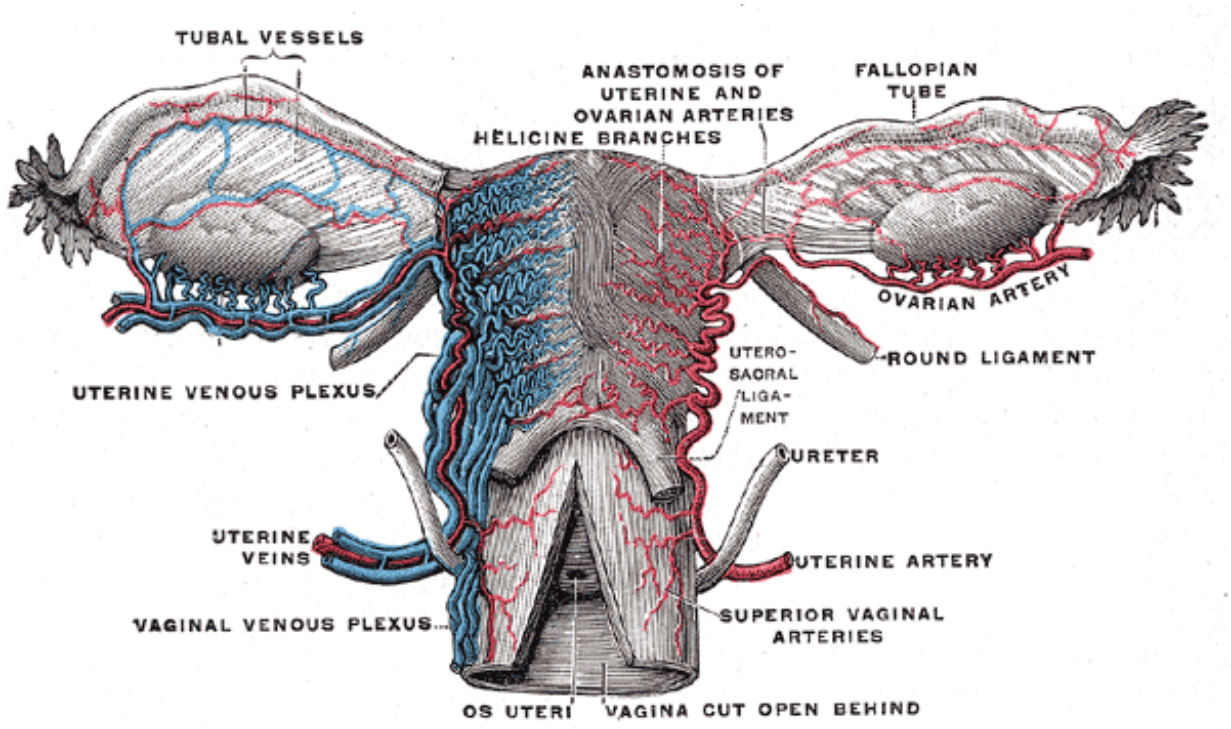

Ovary. Credit: Public Domain

A drug already used to slow tumor growth may also prevent infertility caused by standard chemotherapies, according to a study published online March 6 in the *Proceedings of the National Academy of Sciences*.

Led by researchers from NYU Langone Medical Center, the study in

mice found that the drug everolimus protects ovaries from cyclophosphamide, a chemotherapy used often against breast cancer, but known to deplete the supply of egg cells needed to achieve pregnancy.

Female mice treated with everolimus, along with chemotherapy, were found to have more than twice as many offspring afterward as mice treated with the chemotherapy alone. Such strong results with an available drug, say the study authors, may speed the process of applying for permission to test it in premenopausal cancer patients.

"Our results argue that everolimus may represent a fertility-sparing drug treatment to complement the freezing of eggs and embryos, which are valued methods, but time-consuming, costly, less effective with age, and not protective of long-term ovarian function," says first study author and NYU Langone reproductive endocrinologist Kara Goldman, MD.

Following a four-year residency in obstetrics and gynecology, Goldman pursued a research fellowship with the goal of identifying drugs to address a gap she sees every day as a practicing fertility specialist.

"Patients, including young girls, face devastating choices as they try to balance cancer treatment against their ability to have children in the future," says Goldman, also an assistant professor in the Fertility Center at NYU Langone. "We need more options."

Fertility Protected

The current study results revolve around the ovaries, reproductive organs with a limited supply of "egg cells" capable of carrying genes from a mother to her offspring. Women begin puberty with about 300,000 pre-egg cell groupings called primordial follicles. The field realized 35 years ago that chemotherapy reduces a woman's chances of becoming pregnant, and more recently, that it dramatically shrinks ovarian reserves

and leads to earlier menopause. Solutions have been slow in coming.

In the current study, female mice were treated with cyclophosphamide weekly, and then randomized to also receive either everolimus, an experimental drug called INK128, or nothing. Everolimus and INK128 block the action of the enzyme mTOR, which is part of signaling mechanisms that encourage cell growth. Thus, everolimus is already approved to slow tumor growth in some forms of kidney cancer and breast cancer, but in a different way than chemotherapies. INK128 is an experimental mTOR inhibitor in clinical trials against several cancer types.

Alkylating chemotherapies like cyclophosphamide damage the DNA of rapidly multiplying cells, which enables them to target quickly growing cancers. In recent years, the field learned that cyclophosphamide also turns up mTOR signaling in ovaries, and that mTOR signals cause ovarian follicles to mature and multiply. Thus, cyclophosphamide causes follicular cells to multiply and then attacks their DNA as they do, causing them to self-destruct.

After a literature review revealed that no lab had tried yet it, the study authors decided to see if adding existing mTOR inhibitors everolimus and INK128 to chemotherapy could stop this vicious cycle.

Specifically, the study found that mice treated with chemotherapy combined with either mTOR inhibitor had 7.4 pups on average, while mice treated with chemotherapy alone had 3.4 pups. In addition, mice treated with cyclophosphamide alone saw a 64 percent reduction in their numbers of primordial follicles when compared to control mice, a pattern reversed by mTOR inhibitors. Mouse egg cells use the same steps as their human counterparts to mature, and so make excellent study models. The dose given to the mice was designed to be the rough equivalent of that approved for use in breast cancer patients.

The authors are also committed to answering the question of whether or not this approach may be applicable in general infertility. The ovarian reserve is depleted irreversibly until menopause in all women. The decline is steeper for some women with a condition called primary ovarian insufficiency, which is defined by menopause before the age of 40, even in the absence of chemotherapy. A medication that could extend ovarian function in this wider population would be valuable, and the authors have early data that supports the potential of mTOR inhibitors to extend reproductive lifespan.

Beyond fertility, many women approaching menopause face complications from impaired hormonal function related to follicle loss in aging ovaries, including depression, bone loss, and heart disease.

"Only clinical trial results will tell whether these drugs can protect fertility and counter hormonal deficits naturally by preserving follicles," says senior study author Robert Schneider, PhD, the Albert B. Sabin Professor of Molecular Pathogenesis and associate dean for Biomedical Innovation at NYU Langone. "Our goal is to complete studies on the best dose for ovarian preservation, and then to get everolimus into a trial for this use next year."

More information: mTORC1/2 inhibition preserves ovarian function and fertility during genotoxic chemotherapy,*Proceedings of the National Academy of Sciences*. DOI: 10.1073/pnas.1617233114

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