

Early menopause in mice: A model of human POI

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(Medical Xpress)—Scientists have established a genetic mouse model for primary ovarian insufficiency (POI), a human condition in which women experience irregular menstrual cycles and reduced fertility, and early exposure to estrogen deficiency.

POI affects approximately one in a hundred women. In most cases of primary ovarian insufficiency, the cause is mysterious, although genetics is known to play a causative role. There are no treatments designed to help preserve fertility. Some women with POI retain some ovarian function and a fraction (5-10 percent) have children after receiving the diagnosis.

Having a [mouse model](#) could accelerate research on the causes and mechanisms of POI, and could eventually lead to treatments, says Peng Jin, PhD, associate professor of [human genetics](#) at Emory University School of Medicine.

The results were published online recently in the journal [Human Molecular Genetics](#).

The paper was the result of a collaboration between researchers at Emory and the Institute of Zoology, [Chinese Academy of Sciences](#) in Beijing. Dahua Chen, PhD, associate director of the State

Key Laboratory of [Reproductive Biology](#), is the senior author and postdoctoral fellow Cuiling Lu is the first author. Stephanie Sherman, PhD, professor of human genetics at Emory, is a co-author.

The mouse model builds on research on women who are carriers of a "premutation" for [fragile X syndrome](#), a leading cause of inherited [intellectual disability](#).

The [mice](#) have a fragment of a human [X chromosome](#) from a fragile X premutation carrier. Other non-genetic mouse models used to study menopause include surgical removal of the ovaries, or exposure of mice to a chemical, 4-vinylcyclohexene diepoxide, which depletes the ovaries.

"While the fragile X premutation is a leading cause of POI, I think this model will be useful and relevant for all women with this condition," Jin says.

Women with the fragile X premutation account for around two percent of spontaneous POI cases and 14 percent of familial POI cases. About 20 percent of women who carry the fragile X premutation experience POI, the disorder now called fragile X-associated POI, or FXPOI.

Fragile X syndrome is caused by the expansion of a "triplet repeat" in a gene (FMR1) that is important for signaling in the brain. In fragile X syndrome, the triplet repeat—three DNA letters (CGG) repeated many times—forces the gene to shut off.

For a woman who carries the premutation, the triplet repeat is not large enough to shut the gene off. There is a risk that it will expand in her children enough to generate fragile X syndrome. In addition, the triplet repeat appears to have an effect on the woman's ovaries, independently from its influence on the FMR1 gene.

Jin says studying mice that have an analogous genetic alteration will help scientists understand

what's happening to the ovaries in POI. It appears that the RNA coming from the premutation impairs development of the ovarian follicles, the structures in which eggs/oocytes mature.

The research team found that a quarter of premutation-carrying female mice are infertile. When they are housed with male mice, those that do have pups have them a month later on average (12.5 weeks of age compared to 8.5 weeks), and they have fewer pups.

Puberty occurs at roughly five weeks of age in mice, and the premutation mice have alterations in their ovaries already before puberty. At 25 days of age, there are a reduced number of mature follicles in ovaries of the female mice carrying the premutation. Those mice also have altered levels of hormones resembling those of women with POI, such as elevated FSH (follicle stimulating hormone).

The research team found that in the ovaries of mice with the fragile X premutation, ovulation-related genes are less active. In addition, two cellular signaling pathways (Akt/mTOR) are less active in the [ovaries](#), suggesting that drugs that affect those pathways could be used to treat POI.

More information: Reference: C. Lu et al. Fragile X premutation RNA is sufficient to cause primary ovarian insufficiency in mice. *Hum. Mol. Genet.* (2012) [doi:10.1093/hmg/dds347](https://doi.org/10.1093/hmg/dds347)

Provided by Emory University

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