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Turning down the hormone dial could improve IVF live birth rates

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In a first-of-its-kind study, researchers at Michigan State University are studying ovarian stimulation protocols in cattle and in vitro fertilization in humans simultaneously. The team found the standard practice of using

high levels of hormones to stimulate ovaries is linked to negative outcomes in live birth rates in women and disruptions to ovarian genes in cattle.

The work is a result of a grant from the U.S. Department of Agriculture and the National Institutes of Health.

The goal of using follicle stimulating hormone, or FSH, is to retrieve as many eggs as possible for an IVF cycle in humans or cattle by stimulating the ovarian follicles to mature. The researchers discovered high doses of FSH may not be necessary and may instead disrupt ovarian function and egg quality.

"This research is unique because we are using dairy cattle as a biological model to study what happens as the follicle stimulating hormone dosage is increased," said James Ireland, a professor of animal science in MSU's College of Agriculture and Natural Resources who specializes in cattle reproduction. "The results could benefit both agriculture and human medicine."

The team of researchers was led by Zara Clark, a postdoctoral researcher at the Victoria University of Wellington in New Zealand, while she was a visiting scientist in Ireland's laboratory.

"After analyzing half a million assisted reproductive technology cycle records for women, we saw that, as the clinics added more and more FSH, the live birth rates went down almost 50%," Ireland said. "For the last 15 to 20 years, the FSH doses used on many women is way too high."

This is resulting in what the researchers are calling follicular hyperstimulation dysgenesis, seen for the first time in the bovine (cow) model. The follicles display a severe temporal disruption in the normal

sequence of events. Follicular hyperstimulation dysgenesis is suggested to cause reduced egg retrieval numbers (egg wastage) and decreased live birth rates. The researchers also found a decrease in ovarian function, which may impair IVF and embryo transfer success in cattle.

The discovery of this disruption in follicular development emerged from a technique called RNAseq analysis. This technique enabled the research team to examine most of the genes expressed in the oocyte, or egg, and its surrounding cells in animals that received the industry standard FSH dose compared to those receiving an excessive FSH dose. Previously, it was believed that excessive FSH stimulation could lead to a process called premature luteinization, where the follicle progresses more rapidly than normal to a state of reduced estrogen production and increased production of progesterone and luteinization hormone. Instead, the researchers discovered that most of the follicles in animals receiving excessive FSH doses display abnormal gene expression patterns.

"This indicates that the follicles are 'confused' and do not develop along any previously described or expected pathway," said Keith Latham, a professor of animal science in the College of Agriculture and Natural Resources and research professor in the Department of Obstetrics, Gynecology and Reproductive Biology in the College of Human Medicine.

"Over the last 40 years, about 10 million babies have been born using IVF," Ireland said. "We're at roughly half a million babies by IVF globally and 75,000 to 80,000 in the U.S. each year, and a third of U.S. adults have either used fertility treatments or know someone who has."

Ireland and Latham explain that the work could lead to improved production of high-quality oocytes that can be fertilized and used to generate healthy offspring at a higher rate. This could have implications ranging from refining IVF practices to avoiding negative outcomes that

have taken on an increased importance due to the recent Supreme Court ruling that overturned Roe v. Wade.

The paper was published on July 14, 2022, in the journal *Endocrinology*.

More information: Zaramasina L Clark et al, Follicular Hyperstimulation Dysgenesis: New Explanation for Adverse Effects of Excessive FSH in Ovarian Stimulation, *Endocrinology* (2022). DOI: 10.1210/endocr/bqac100

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