Common equine painkiller disrupts assisted reproduction technique efficiency in mares

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Researchers at the Texas A&M School of Veterinary Medicine & Biomedical Sciences (VMBS) have discovered that phenylbutazone, a non-steroidal anti-inflammatory drug (NSAID) commonly prescribed in horses, can affect the ability of a mare's egg cells—called "oocytes"—to become viable embryos, which is a crucial step in assisted reproduction

in horses.

This discovery, recently published in the journal *Theriogenology*, is significant because of the time and money that horse owners often invest in assisted reproduction.

Just like humans, horses sometimes need help from science in order to reproduce. When they do, special steps are needed for a successful pregnancy because of the unique properties of equine sex cells.

"In horses, the process of in-vitro fertilization (IVF) is more complex than it is in humans," said Dr. Luisa Ramirez-Agamez, a Ph.D. candidate in the VMBS Department of Large Animal Clinical Sciences (VLCS) studying equine reproduction. "First, a mare's oocytes need approximately 30 hours to mature in the laboratory once they have been collected before they can be fertilized. Then, we have to inject the eggs with sperm to induce fertilization, a process known as intracytoplasmic sperm injection (ICSI).

"We discovered that phenylbutazone, commonly known as bute, can affect both the ability of a mare's eggs to mature correctly when cultured and whether the fertilized eggs will develop into a viable embryo," she explained. "In either of those cases, the eggs affected by bute cannot be used in assisted reproduction."

The value of equine assisted reproduction

Assisted reproduction is an important resource for many horse owners, especially those who make a living from their herds. Many horse owners also care deeply about producing offspring from their favorite horses in order to carry on their legacies.

In some cases, mares who are chronically lame and unable to support a

pregnancy themselves may become egg donors, with their eggs fertilized in a laboratory and carried to term by a surrogate.

"This is one of the specific situations impacted by our discovery," Ramirez said. "Mares who are chronically lame are likely going to be on bute because it helps with pain management—especially in the musculoskeletal system—which, according to our results, will hinder their ability to participate in assisted reproduction programs.

"In a future study, we hope to determine an alternative to bute that supplies the same level of pain management but does not interfere with reproduction," she said.

The good news is that bute's effect on equine oocytes appears to wear off within a few weeks.

"We collected the eggs at three days post-treatment, then 33 days, and then 77 days," she said. "We found that eggs collected three days after administration of bute were not able to produce embryos, but those collected at 33 days were successful. We hope to find a more exact answer in terms of how bute affects egg cell quality in a future study."

Implications for human medicine

Looking to the future, Ramirez is interested in collaborating with researchers in human medicine because of the possible implications of her discovery for IVF in women.

"NSAIDs are often given to women during IVF to slow down their ovulation cycle, which is the ovaries' release of an egg each month," she explained. "Under normal circumstances, most women only produce one egg cell each month, but IVF is expensive and time-consuming, so women are given hormones that cause them to produce more than one

egg each cycle. This way, there is more than one egg to collect. NSAIDs help prevent women from ovulating early so they don't lose those eggs."

But after her recent discovery about NSAIDs and horse reproduction, Ramirez wonders if NSAIDs could also have unknown negative effects on IVF.

"NSAIDs are generally thought to have a positive impact on IVF in women, but our results suggest that these drugs are not as benign for reproduction in horses," Ramirez said. "Some NSAIDs, like banamine, actually cause anovulatory follicles in horses—follicles in the ovaries that don't release egg cells during ovulation as they are supposed to.

"This is not the case in women, and so NSAIDs are thought to be safe. But now we know that bute can actually keep fertilized eggs from becoming embryos, and it's possible that some NSAIDs could have a similar effect in women," she said. "This is something I want to find out."

More information: Luisa Ramírez-Agámez et al, Treatment of mares with the non-steroidal anti-inflammatory drug (NSAID) phenylbutazone transiently affects in vitro maturation of equine oocytes and blastocyst development after Intracytoplasmic Sperm Injection (ICSI), *Theriogenology* (2024). DOI: 10.1016/j.theriogenology.2024.04.017

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