Analyzing the impact of ovulation-inducing agents on the quality of embryo

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Some experts advocate the use of ovulation-inducing agents to collect multiple eggs from the ovaries in one go. However, there is an ongoing debate on whether this approach can produce high-quality eggs for *in vitro* fertilization. In this study, researchers used a mouse model and a state-of-the-art live-cell imaging technique to observe the development and chromosome segregation of fertilized eggs. Credit: "Oocyte with Zona pellucida" by ZEISS Microscopy

Low birth rates have become a serious problem in many developed countries throughout the world, with Japan being a prime example. In Japan particularly, aging and stress have led to a massive rise in infertility, which now affects one in every 4.4 couples.

To find a workaround for this condition, many couples have now turned to assisted reproduction technologies (ARTs) and in vitro fertilization (IVF) for conception. However, even though ARTs and IVF methods are well-established and have been widely used for over four decades, birth rates post IVF in Japan are still critically low, peaking at a meager 10.2%.

One of the reasons behind the low success of IVF is closely related to the quality of the eggs or "oocytes" collected from the ovaries. Today, there are two main approaches in clinical practice to obtain oocytes—the first being the stimulated cycle method and the other being the natural cycle method.

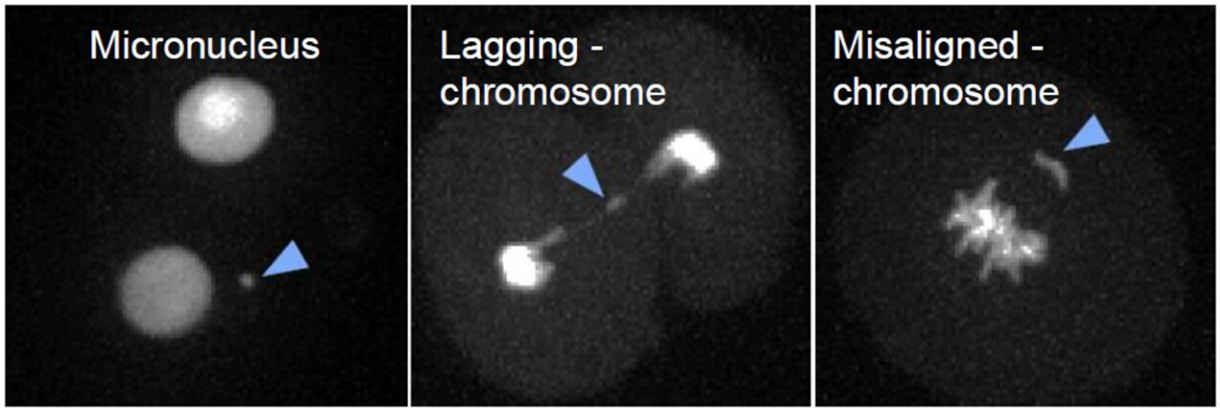
In the stimulated cycle method, the patient is administered ovulation-inducing agents orally or through multiple injections. This enables doctors to extract multiple mature oocytes in one go. In contrast, the natural cycle method avoids or uses minimal administration of inducing agents, and typically only one or two oocytes can be collected per month as a part of the natural ovulation cycle.

However, there is an ongoing debate regarding which method is better. This is important because not only does this impact couples differently, but also, there is no firm evidence on whether the ovulation inducing method affects the quality of the embryo.

Now, to address this knowledge gap, a research team from Japan conducted a study using an animal model to pry into the differences between oocytes collected using natural and stimulated approaches. This

study was published in the *Journal of Reproduction and Development* and was conducted by Professor Kazuo Yamagata from the Faculty of Biology-Oriented Science and Technology (BOST), Kindai University, embryologist Mayuko Kurumizaka from Yokohama City University, Dr. Tatsuma Yao from Fuso Pharmaceutical Industries, Ltd., and Dr. Mikiko Tokoro from Asada Ladies Clinic.

Sharing the motivation behind their study, Prof. Yamagata explains, "Although the influence of ovarian stimulation on embryo quality has been described, this issue remains controversial. Here, we analyzed the influence of ovarian stimulation on developmental speed and chromosome segregation using live-cell imaging."



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The experimental protocol involved establishing two groups of female mice to collect oocytes from. The "stimulated group" was treated with ovulation-inducing agents whereas the other "non-stimulated group" was not given any drugs. Next, all the viable oocytes were fertilized using sperm obtained from a single male mouse, and the development of the embryos were monitored by live-cell imaging.

Initial experiments confirmed that the stimulated mice produced roughly 1.4 times more viable oocytes than the non-stimulated mice. Then, to assess developmental abnormalities in the fertilized oocytes, the researchers employed a novel live-cell imaging technique, which had been previously developed by the team to perform long-term observations of preimplantation embryos.

By injecting the embryos with small amounts of RNA encoding a fluorescent protein, intracellular processes of some embryos could be observed. This approach enabled the visualization of embryonic development in a near-natural state.

Detailed observations of the developing embryos revealed no significant differences between both groups, suggesting that stimulation did not adversely affect the formation and distribution of chromosomes, or the process of cell multiplication. Interestingly, the researchers noted that initial cellular divisions were slightly faster in embryos produced from stimulated oocytes, leading to faster development. This is important since faster initial development can translate into higher chances of successful implantation.

Taken together, the results indicate that the stimulated cycle method is a viable technique to collect more number of oocytes than the natural cycle method and has no adverse effect on the quality of eggs. Although further research is needed in this domain, the research team expects their findings to have important implications in the future of fertility science.

"Our study provides fertility clinics and patients with useful information that will help them decide whether to pursue ovarian stimulation or not," concludes Prof. Yamagata.

More information: Mayuko KURUMIZAKA et al, Effect of ovarian stimulation on developmental speed of preimplantation embryo in a mouse model, *Journal of Reproduction and Development* (2024). DOI: 10.1262/jrd.2023-089

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