Cilostazol improves oocyte competence and IVF outcomes in mice: ovulation of immature oocytes with higher developmental rates

Abstract

Study question: Can temporal arrest of oocyte maturation in superovulated mice synchronize oocyte meiotic and cytoplasmic maturation and improve oocyte competence and IVF outcomes?

Summary answer: Temporal arrest of oocyte maturation in vivo results in synchronization of oocyte meiotic and cytoplasmic maturation. The latter was observed to improve IVF outcomes and oocyte competence in superovulated mice. What is known already: Temporal arrest of oocyte meiotic maturation in vitro, using phosphodiesterase 3A (PDE3A) inhibitors, can synchronize cytoplasmic and meiotic maturation and improve IVF outcomes. However, the beneficial effect of in vivo synchronization of oocyte maturation on IVF outcomes has not yet been addressed. Cilostazol is a PDE3A inhibitor with an established record of safe long-term use in patients. Cilostazol caused mice to ovulate immature oocytes at different stages based on time, dose, or frequency of administration. Study design, size, duration: This study was designed as a mouse superovulated model for women undergoing hyperstimulation and IVF. No less than 10 mice were used in each group. This study was started in 2012 and finished in 2014. Participants/materials, setting, methods: Swiss Webster mice were used in this study, and all materials were purchased

from Sigma (St. Louis, MO). This study was of university laboratory setting and as follow: Ovulated or ovarian mature or immature oocytes were collected from superovulated mice treated with different doses of cilostazol. Main results and the role of chance: Ovulated germinal vesicle (GV) oocytes had significantly higher rates of advanced chromatin configuration and cortical granule distribution than did ovarian GV oocytes collected from large antral follicles of hyperstimulated mice. Ovulated GV oocytes had lower levels of cAMP and consequently higher rates of germinal vesicle breakdown, first polar body emission, in vitro fertilization (IVF), and blastocyst formation than did ovarian GV oocytes ($P < 0.0001$). Ovulated MI oocytes had higher rates of normal spindles and chromosomes aligned at the metaphase plates than did ovarian MI oocytes collected from preovulatory follicles of superovulated mice ($P < 0.003$). Mice ovulating MI oocytes produced litter sizes greater than those observed in control mice ovulating mature oocytes ($P < 0.002$). Limitations, reason for caution: The positive impact of CLZ on oocyte matu- ration and IVF outcomes need to be confirmed using other animal models that are more predictive to human reproduction. Wider implications of the findings: The ovulated immature oocytes may substitute for ovarian immature oocytes and become an additional research re- source. More importantly, the capability of a clinically approved medication to increase oocyte fertilization rates and litter sizes in mice, at doses extrapolated from human therapeutic doses, suggests the potential

scenario of the inclusion of CLZ in human hyperstimulation programs to increase the live birth rate of IVF babies. Study funding/competing interest(s): Funding by University(ies). Funding by hospital/clinic(s) – Texas A&M University and BARZ IVF Center for Embryo Research and Infertility Treatment.