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Title: FACTORS ASSOCIATED WITH THE REPRODUCTIVE POTENTIAL OF VITRIFIED-WARMED, AUTOLOGOUS OOCYTES DERIVED FROM ELECTIVE OOCYTE CRYOPRESERVATION CYCLES

Study Question: What clinical factors are associated with optimal cryopreserved oocyte survival, fertilization, embryo culture, and transfer outcomes?

Summary Answer: The outcome of autologous oocyte vitrification-warming cycles is optimized in younger patients who undergo transfer of blastocyst-stage embryos.

What is known already: In an effort to protect against the age-related decline in fertility, women electively undergo oocyte cryopreservation to enhance their ability to conceive when they are ready. While enhancements in cryopreservation methodology, including advances in vitrification techniques, have demonstrated the efficacy of elective oocyte cryopreservation as a means of fertility preservation, a relatively small proportion of women have returned to utilize their vitrified oocytes. Current data related to efficacy is limited to extrapolations from hypothetical models and case series. Given the paucity of experience, physicians seek prognostic information to guide and counsel patients and manage expectations regarding the likelihood of success from frozen oocytes.

Study design, size, and duration: This retrospective cohort study includes 1197 patients who underwent 1396 oocyte vitrification cycles, from 2010 to 2017. One hundred and eleven patients (9.3%) returned for oocyte warming (n= 118) and treatment. Fresh (n=52) and frozen (n=39) transfers of cleavage (n=37) or blastocyst stage (n=54) embryos were observed. Over half of the patients (52.3%) who warmed their

oocytes were successful in creating embryos eligible for preimplantation genetic testing (PGT), that were then vitrified for future use.

Participants/materials, setting, methods: Patients presented to a private IVF clinic for elective oocyte cryopreservation. Cycles in which autologous, vitrified oocytes were warmed (n=118) were analyzed using multivariate linear and binary logistic regression models to assess patient demographics (age, BMI, and AMH); and treatment related factors (number of oocytes cryopreserved) associated with oocyte survival and clinical outcome. The influence of these factors and the treatment approach (i.e. PGS, frozen embryo transfer (FET)) on embryo transfer success was determined.

Main results and the role of chance: 1015 oocytes were thawed and fertilized using ICSI. 63.3% of fertilized eggs reached cleavage stage, and 39.0% reached blastocyst stage. Chemical and clinical pregnancies were achieved in 52.7% (n=48/91) and 41.8% (n=38/91) of cycles, respectively. Increased oocyte age ($\beta = -0.6$, $p=0.0003$) and decreased AMH ($\beta = -1.4$, $p<0.0001$) reduced the number of oocytes available for warming, but not the rate of survival. Controlling for age, each additional oocyte warmed was associated with an increase in the rate of oocyte survival ($\beta = 0.007$, $p=0.04$), embryos reaching the cleavage ($\beta = 0.008$, $p=0.01$) and blastocyst stage ($\beta = 0.008$, $p<0.0001$) and being amenable to PGT (OR 1.182 [95% CI 1.051-1.33], $p=0.005$) and vitrification (OR 1.212 [95% CI 1.048-1.403], $p=0.009$). Oocyte age ($\beta = -0.02$, $p=0.02$) and AMH ($\beta = 0.05$, $p=0.03$) modified the rate of blastulation. The odds of having an embryo available for fresh transfer was independent of age, AMH or the number of oocytes warmed. Controlling for confounders (age, AMH, BMI, oocytes warmed, embryo stage, PGT, FET, embryos transferred and endometrial thickness), clinical pregnancy rate was negatively impacted by increased oocyte age (OR 0.78 [95% CI 0.60-1.01], $p=0.059$) and transfer of cleavage embryos (OR 0.10 [95% CI 0.01-1.05], $p=0.05$).

Limitations, reasons for caution: This analysis is retrospective and subject to confounding bias. Prospective randomization of patients to various treatment approaches (ie. transfer of day 3 vs. day 5 and screened vs. unscreened embryos) would ultimately validate our findings and define the optimal strategy for patients utilizing vitrified-warmed oocytes.

Wider implications of the findings: Women who desire to electively preserve their fertility should be encouraged to vitrify their oocytes at a younger age to increase their probability of achieving future pregnancy. When possible, zygotes from warmed oocytes should undergo extended culture and be transferred at the blastocyst stage to optimize embryo selection and improve clinical outcome.

Study funding/ competing interests: Not applicable

Trial registration number: This study was approved by the Western Institutional Review Board (Study Number: 1167398).