Title: CAN HIGH MARKERS OF OVARIAN RESERVE OVERCOME THE USUAL AGE-RELATED DECLINE IN EUPLOIDY IN IVF-PGS CYCLES IN WOMEN OVER AGE 40?

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Study Question (25): Are patients over 40 with average or above-average baseline markers of ovarian reserve protected against the typical age-related increase in aneuploidy?

Summary Answer (25): Women with high markers of ovarian reserve and those with polycystic ovary syndrome (PCOS) retain a meaningful chance of obtaining a euploid embryo even at age 44 and beyond.

What is Known Already (100): Advanced reproductive age increases the likelihood of poor ovarian response and aneuploidy. Prior data suggests that there may be an age threshold beyond which above-average markers of ovarian reserve no longer increase viable pregnancy rates in in-vitro fertilization (IVF) cycles without preimplantation genetic screening (PGS).

Study design, size, duration (75): Retrospective cohort study of IVF-PGS cycles at an urban academic fertility center from 2013-2016.

Participants/materials, settings, methods (75): IVF-PGS cycles for women aged 40 and above using autologous oocytes were included. The cycle protocol was determined by the individual physician. PGS was performed using qPCR and Next Generation Sequencing of trophectoderm biopsies on expanded blastocysts. Descriptive statistics, Pearson's correlation, Mann-Whitney U and Kruskal-Wallis tests were computed as appropriate using Stata v12.1 (College Station, TX).

Main results and the role of chance (200): Of 990 IVF-PGS cycles included, 45.8% resulted in at least one euploid embryo; only about 5% yielded more than 2. The numbers (%) of cycles resulting in no euploid embryo were as follows: 129/330 (39.1%) for 40yo, 113/236 (47.9%) for 41yo, 118/194 (60.8%) for 42yo, 97/130 (74.6%) for 43yo, and 80/100 (80.0%) for 44yo and above. In each age category, the median anti-Müllerian hormone (AMH) level for those with at least one euploid embryo was substantially higher than age-based averages, ranging from 1.2-1.8 ng/mL; the median antral follicle count (AFC) in these women ranged from 8-10. AMH ($p<0.001$) and AFC ($p<0.001$) were higher, and day 3 follicle-stimulating hormone (FSH) ($p<0.02$) lower, in those women with a euploid embryo. However, AMH had the strongest correlation ($\rho=0.39$, $p<0.001$) with the number of euploid embryos and was most consistent across age groups, followed by AFC ($\rho=0.31$, $p<0.001$) and then FSH ($\rho=-0.10$, $p=0.003$). Body mass

index did not correlate with count of euploid embryos. Women with PCOS had a significantly higher median number (p=0.01) of euploid embryos, 1 [0,2] versus 0 [0,1] for non-PCOS women.

Limitations, reasons for caution (50): The study was retrospective in nature, and certain confounders, such as ethnic background, may remain unaccounted for. As we move toward exclusive testing via a next-generation sequencing platform, it is possible that more embryos will be found to have some degree of aneuploidy, potentially changing the results reported here.

Wider implications of the findings (50): The age-related increase in aneuploidy is inevitable. However, women with ovarian reserve markers exceeding age-based averages retain a substantial chance of obtaining a euploid embryo despite advanced reproductive age. IVF-PGS in this population allows for identification and selective transfer of embryos with increased potential to develop into viable pregnancies.

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Trial registration number: not applicable