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Title:

FRAGILE X CARRIERS WITH CGG REPEATS IN THE INTERMEDIATE AND PREMUTATION RANGE EXHIBIT DIMINISHED OVARIAN RESERVE BUT ARE NOT AT RISK OF INCREASED EMBRYONIC ANEUPLOIDY

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Objective:

Female fragile X carriers with CGG triplet repeats in the intermediate to premutation range are known to be at risk for decreased ovarian reserve and premature ovarian aging, yet whether they experience an increased rate of embryonic aneuploidy remains uncertain. Carriers may utilize PGT to prevent transfer of embryos affected by Fragile X, while concomitantly evaluating their embryos for the presence of aneuploidy. This study sought to understand if decreased ovarian reserve in fragile X carriers translates into an increased incidence of embryonic aneuploidy.

Design:

Retrospective, observational study

Materials and Methods:

The study included all fragile X carrier patients who had CGG repeats in the intermediate and premutation range and underwent IVF with PGT from January 2012 to March 2017. Aneuploidy screening was performed by trophectoderm biopsy on day 5 to 7 of embryo development, using polymerase chain reaction (PCR) or next generation sequencing (NGS). The association between the number of CGG repeats and baseline demographic factors, ovarian reserve markers, IVF cycle characteristics and PGT results was evaluated. Multivariate linear regression analyses were

performed to investigate the relationship between the rate of aneuploidy and the number of CGG triplet repeats.

Results:

Twenty-eight patients with an abnormal number of fragile X CGG repeats underwent 43 IVF cycles with PGT. Descriptive statistics outlining baseline demographic factors, ovarian reserve markers, cycle characteristics and aneuploidy screening results and correlation with the number of CGG repeats are shown in Table 1. When controlling for age, AMH, day 3 FSH, BAFC, the number of CGG repeats was not significantly associated with the degree of aneuploidy (β = 0.218 [95% CI -0.011-0.019], p=0.21) or euploidy (β = 0.-0.285 [95% CI -0.024-0.012], p=0.37). The number of CGG repeats had a significant positive correlation with day 3 FSH levels and a significant negative correlation with AMH, basal antral follicle count (BAFC) and day 3 & 5 embryos counts.

Conclusion:

While this study contributes to the growing body of literature suggesting a correlation between the number of CGG repeats in the intermediate and permutation range and diminished ovarian reserve, it is the first to show that there is no affect on the likelihood of embryonic aneuploidy. The findings suggest that the diminished ovarian reserve seen in fragile X carriers is more quantitative than qualitative and may arise via a mechanism distinct from that in women with age-related ovarian decline.

Support:

None

Table 1:

	Mean Standard Deviation	Range	Correlation with number of CGG repeats	P value
Number of CGG repeats	66.7 ± 15.0	45.0-97.0	--	--
Age	33.6 ± 4.3	24.5-41.0	-0.59	0.0014
BMI	23.9 ± 4.2	18.6-36.0	-0.17	NS
Day 3 FSH	6.2 ± 3.1	0.7-15.0	0.66	0.0003
AMH	3.3 ± 2.9	0.2-13.0	-0.47	0.0161
BAFC	11.8 ± 5.0	5.0-22.0	-0.42	0.0306
Estradiol at surge	2218.0 ± 948.1	687.0-4796.0	-0.20	NS
Eggs Retrieved	14.1 ± 6.2	3.0-26.0	-0.19	NS

Mature Oocytes	11.2 ± 4.5	3.0-20.0	-0.35	NS
Day 3 embryos	9.2 ± 3.7	2.0-14.0	-0.42	0.0322
Blastocyst count	6.9 ± 3.5	1.0-14.0	-0.45	0.0223
Embryos biopsied	5.6 ± 2.8	1.0-12.0	-0.13	NS
Proportion of aneuploidy embryos	--	--	-0.24	NS
Proportion of euploid embryos	--	--	0.06	NS