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Title:
Ovarian Reserve and Embryonic Aneuploidy Rates in BRCA 1 and 2 carriers

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Objective:
Prior studies have reported reduced ovarian reserve and higher rates of infertility in BRCA 1 mutation carriers. The impaired ability of the mutated BRCA gene to repair double-strand breaks in DNA may prompt oocyte aging, apoptosis and meiotic errors. Although a link between BRCA mutations and decreased ovarian reserve has been hypothesized, the relative severity of each gene mutation on reproductive potential has not been defined. Furthermore, no prior studies have assessed the rate of embryonic aneuploidy in patients who carry the BRCA mutation.

Design:
Retrospective cohort study

Materials and Methods:
Patients with a BRCA mutation underwent controlled ovarian hyperstimulation (COH), from June 2009 to April 2016. Basic demographic and cycle characteristics were compared among the BRCA 1 and BRCA 2 cohorts (Table 1). Blastulation rate was calculated as the number of day 5 blastocysts of the total number of fertilized oocytes in a cycle. Both cohorts included cycles in which embryos underwent preimplantation genetic screening (PGS) (via trophectoderm biopsy of blastocysts) for both BRCA and chromosome copy number. Data was analyzed using student's t-test, chi-square and linear regression.

Results:
A total of 42 IVF cycles for fertility treatment (n=35) and oocyte cryopreservation (n=7) were included. BRCA 1 (n=25) and 2 (n=17) carriers were similar in age and BMI. Ovarian reserve, represented by mean day 3 FSH levels, was similar between cohorts. There was an increased rise in day 3 FSH in BRCA 1 vs. BRCA 2 carriers (0.39 vs. 0.14) per each additional year in patient age. There was a greater decrease in number of eggs retrieved in BRCA 1 carriers (-2.5

vs. -1.0) for every unit increase in day 3 FSH. Study groups were stimulated with equivalent cumulative gonadotropin dosages and had similar oocyte yield, fertilization and blastulation rates. PGS was utilized in 16 cycles for BRCA 1 (n=9) and BRCA 2 (n=7) patients, revealing similar rates of aneuploidy (43.9% vs. 42.9%, P<0.05).

Conclusions:

A trend toward accelerated age-related decline in ovarian reserve and oocyte yield was demonstrated in BRCA 1 carriers. Despite this, all patients had oocytes retrieved and blastocysts available for biopsy. Although patients who carry the BRCA mutation are known to have an altered DNA repair mechanism, their embryos did not demonstrate increased aneuploidy. Given the low incidence of the mutation, multi-center studies on BRCA mutation carriers who utilize PGS are needed to corroborate these preliminary findings.

Support:

None

Table 1:

	BRCA 1	BRCA 2	P value
Number of patients	25	17	
Age*	35.8 ± 4.3	35.7 ± 3.6	NS
BMI*	23.2 ± 3.3	26.0 ± 5.2	NS
Day 3 FSH*	7.5 ± 4.0	7.2 ± 3.9	NS
Cumulative gonadotropin dose*	2638.4 ± 1055.82	3470.2 ± 1364.21	NS
Eggs Retrieved*	23.0 ± 15.0	15.0 ± 7.6	NS
Fertilization rate	77.3% (150/194)	81.0% (94/116)	NS
Blastocysts per patient*	8.5 ± 10.4	6.6 ± 6.0	NS
Blastulation rate	61.2% (93/152)	69.5% (66/95)	NS
Total blastocysts for PGT	66	35	NS
Aneuploidy rate	43.9% (29/66)	42.9% (15/35)	NS

*Expressed as mean ± standard deviation