American Society for Reproductive Medicine 2018 Scientific Congress & Expo
October 6 to 10, 2018 Denver, CO, USA

Title:

HOW DO OVARIAN RESERVE AND ANEUPLOIDY IN BRCA CARRIERS COMPARE TO THAT OF THE GENERAL POPULATION UNDERGOING ART?

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Objective:

BRCA1 and BRCA2 play an integral role in DNA mismatch repair. Patients who express a BRCA mutation have been shown to accumulate damaged DNA, which may stimulate oocyte aging and/or depletion.[1] Limited studies have assessed the relationship between BRCA carrier status with ovarian reserve, response to controlled ovarian hyperstimulation (COH), and rate of embryo aneuploidy. The literature is divided regarding AMH levels, with some studies associating BRCA1 and others BRCA2 to reduced AMH.[2,3] Additionally, reports on BRCA1/2 response to stimulation, oocyte yield, and fertilization rate remain conflicted.[4,5] No studies to date have examined rates of aneuploidy in BRCA1 and 2 carriers in an age controlled comparison. The objective of this study was to evaluate cycle outcomes of BRCA1/BRCA2 patients who undergo assisted reproductive technologies (ART) treatment.

Design:

Retrospective cohort analysis

Materials and Methods:

The study included patients who underwent COH for IVF or oocyte cryopreservation between 2002 and 2018. Patients who were identified as carriers of BRCA1 or BRCA2 mutation were compared to patients who did not report having BRCA1/2 carrier status. Outcomes included patient age, AMH, BAFC, number of mature oocytes retrieved per cycle, fertilization, blastulation, and aneuploidy rates. Student's t-test, chi square, and multivariate linear regression were used for statistical analysis. A mixed model was utilized to account for patients undergoing multiple cycles.

Results:

A total of 80 BRCA1 and 44 BRCA2 patients were compared to 15,749 controls. Patient demographics, ovarian reserve, ovarian response to gonadotropic stimulation, and IVF laboratory outcomes, comparing BRCA1/BRCA2 carriers with controls were reviewed (Table 1). BRCA1 carriers were significantly younger than the control population, (35.2 vs. 37.0, p=0.03). Controlling for age, AMH was not reduced in BRCA1 (β=-1.6, p=0.82) and BRCA 2 carriers (β=-3.9, p=0.67) as compared with controls. BAFC, however, was significantly reduced in BRCA1 carriers (β=-2.5, p=0.02) when controlling for age. BRCA2 carriers also trended towards having a reduced BAFC ((β=-2.4, p=0.07) as compared with the control group. Controlling for age and AMH, the number of oocytes retrieved was significantly reduced in

BRCA1 carriers (β=-4.5, p=0.02); however, BRCA2 carriers had a similar number of oocytes retrieved as compared with controls (β=-1.7, p=0.49). Controlling for age, fertilization rate was not modified in BRCA carriers, however, there was a trend towards decreased blastulation rate in BRCA1 (β=-0.15, p=0.07) and BRCA2 carriers (β=-0.17, p=0.06). Controlling for age, aneuploidy rate was not modified in BRCA1 (β=0.1, p=0.26) and BRCA2 carriers (β=0.5, p=0.64).

Conclusions:

BRCA patients commonly undergo IVF and egg freezing and at an earlier age, most likely due to the recommendation for prophylactic salpingo-oophorectomy by age 35 to 40. Despite the subtle decrease in ovarian reserve and trend towards reduced blastulation rate seen in BRCA carriers, embryo quality, as measured by aneuploidy, was not affected. BRCA carriers undergoing COH for IVF or oocyte cryopreservation can be reassured that they will have outcomes comparable to the general population undergoing ART and of the achievability of their goals to grow their family.

Support:

None

Table 1: Comparison of BRCA 1 and BRCA 2 carriers with controls – patient demographics, ovarian reserve, cycle characteristics and controlled ovarian hyperstimulation outcome.

	BRCA 1	BRCA 2	Controls	p value

Patients	80	44	15749	--
COH cycles	33	22	24681	--
Age	35.2 +/-3.8	35.5 +/- 3.7	37.0 +/- 4.6	0.03*
AMH	5.1 +/- 5.4	6.9 +/- 17.1	2.8 +/- 30.8	NS
BAFC	13.7 +/- 6.9	13.7 +/- 8.4	10.2 +/- 6.2	0.002*
Cumulative gonadotropin dose	3390.5 +/- 1258.6	3638.1 +/- 1499.7	3733.1 +/-1366.3	NS
E2 at surge (pg/ml)	1877.6 +/- 1313.7	1241.0 +/- 1011.6	2062.9 +/-1097.8	0.0004**
Oocytes retrieved	18.0 +/- 12.9	14.1 +/- 8.7	13.4 +/- 8.5	0.002*
Mature oocytes retrieved	11.3 +/- 14.0	8.4 +/- 9.2	10.2 +/- 7.9	NS
Fertilization rate	74.3% (277/373)	70.8% (131/185)	67.7% (170,313/251,450)	0.007*
Day 3 embryos	7.3 +/- 11.1	5.6 +/- 8.1	5.0 +/- 5.8	0.03*
Day 5 embryos	5.2 +/- 8.1	4.1 +/- 6.4	3.2 +/- 4.3	0.007*
Blastulation rate	61.7% (171/277)	68.7% (90/131)	45.8% (77,974/170,313)	<0.0001*,**
Aneuploidy rate	36.2% (42/116)	23.1% (12/52)	44.2% (11,929/26,994)	0.002**

Note: Only significant p values reported, denoted by * for BRCA1 vs. controls and ** for BRCA2 vs. controls

References:

1. Scully R, Livingston DM. In search of the tumour-suppressor functions of BRCA1 and BRCA2. Nature. 2000;408(6811):429-432

2. Phillips K-A, Collins IM, Milne RL, McLachlan SA, Friedlander M, Hickey M, et al. Anti-Müllerian hormone serum concentrations of women with germline BRCA1 or BRCA2 mutations. Human Reproduction. 2016:dew044.

3. Johnson L, Sammel MD, Domchek S, Schanne A, Prewitt M, Gracia C. Antimüllerian hormone levels are lower in BRCA2 mutation carriers. Fertility and Sterility. 2017;107(5):1256-65.

4. Derks-Smeets IA, van Tilborg TC, van Montfoort A, Smits L, Torrance HL, Meijer-Hoogeveen M, et al. BRCA1 mutation carriers have a lower number of mature oocytes after ovarian stimulation for IVF/PGD. Journal of Assisted Reproduction and Genetics. 2017;1-8.

5. Shapira M, Raanani H, Feldman B, Srebnik N, Dereck-Haim S, Manela D, et al. BRCA mutation carriers show normal ovarian response in in vitro fertilization cycles. Fertility and Sterility. 2015;104(5):1162-1167.