ASSOCIATION BETWEEN HEREDITARY BREAST CANCER GENE VARIANTS AND ANEUPLOIDY RATES IN IVF PGT-M CYCLES

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Background:
Hereditary breast cancer genes cause defects in the homologous recombination repair (HRR) pathway which lead to tumorigenesis and are some of the most tested single gene disorders in patients utilizing preimplantation genetic testing for monogenic disorders (PGT-M). The HRR pathway is also central to meiosis and contributes to gamete genetic diversity. While HRR is central to both breast cancer development and meiotic recombination, it is unknown whether single gene disorders involved in HRR confer an increased risk of aneuploidy during in vitro fertilization.

Objective:
To assess aneuploidy rates in cycles utilizing preimplantation genetic testing for aneuploidy (PGT-A) and PGT-M for autosomal dominant hereditary breast cancer genes involved in HRR compared to cycles utilizing PGT-A alone.

Materials and Methods:
All IVF cycles for patients aged 18-45 undergoing PGT-A using next generation sequencing from trophectoderm biopsies with or without concurrent PGT-M at a single genetics laboratory were analyzed from November 2019 through March 2023. All cycles utilizing PGT-M for *BRCA1, BRCA2, TP53, ATM, PALB2, and CHEK2* were included as these are commonly tested autosomal dominant hereditary breast cancer genes involved in HRR. Any embryos without both PGT-A and PGT-M results were excluded. Cycles were stratified by SART age categories: <35, 35-37, 38-40, 41-42, and >42. Embryos were classified as euploid, aneuploid, and mosaic (40-80%). Primary outcome was aneuploidy rate per cycle in patients < 35 years of age. Comparative analyses were performed using Chi-square and median tests.

Result(s): A total of 68,682 IVF cycles were included in the final analysis, with 415 cycles (0.6%) utilizing PGT-A + PGT-M testing for autosomal dominant breast cancer genes involved in HRR and 68,267 cycles (93.8%) utilizing PGT-A testing only. The breast cancer HRR genes included in the analysis were *BRCA1* (55.3%), *BRCA2* (29.7%), *TP53* (4.7%), *ATM* (3.5%), *PALB2* (2.1%), and *CHEK2* (1.9%). In the <35 years of age group, there was no significant difference in aneuploidy rates between the PGT-A + PGT-M group compared to the PGT-A alone group. Similarly, no significant difference was noted in the other age groups, except in the 43-45 years of age group (p=0.019). However, this age group accounted for only 4 (1%) of the PGT-A + PGT-M cycles compared to 9,138 cycles (13.4%) in the PGT-A alone group, likely explaining the statistical significance. There was also no significant difference in mosaicism between the two groups after stratifying by age, which is expected as the mechanism of mosaicism relates to mitotic errors and thus, should not be impacted by defects in HRR (Table 1).

Conclusions: While the HRR pathway is central to both meiotic recombination and tumorigenesis in certain hereditary breast cancers, there does not appear to be an increased rate of aneuploidy in cycles that have embryos for PGT-A and PGT-M testing of autosomal dominant breast cancer gene variants.

Financial Support: None

References:

Table 1. Aneuploidy rate of PGT-A + PGT-M for HRR breast cancer genes compared to PGT-A only controls stratified by SART age.

	N (number of cycles) Mean (95% CI)		
	PGT-A + PGT-M	**PGT-A alone**	**Median p-value**
<35	249	20,823	
Aneuploid	29.4% (0.259 – 0.330)	28.3% (0.279 – 0.287)	0.533
Mosaic	7.8% (0.059 – 0.098)	7.5% (0.073 – 0.077)	0.715
35-37	74	10,679	
Aneuploid	32.3% (0.260 – 0.387)	36.0% (0.355 – 0.366)	0.668
Mosaic	8.5% (0.038 – 0.132)	7.8% (0.075 – 0.081)	0.739
38-40	70	16,947	
Aneuploid	42.9% (0.354 – 0.503)	48.0% (0.475 – 0.485)	0.387
Mosaic	5.4% (0.026 – 0.081)	6.9% (0.067 – 0.072)	0.965
41-42	18	10,680	
Aneuploid	52.8% (0.294 – 0.762)	62.9% (0.623 – 0.636)	0.623
Mosaic	10.6% (-0.023 – 0.234)	6.2% (0.059 – 0.066)	0.600
43-45	4	9,138	
Aneuploid	55.4% (0.383 – 0.724)	74.2% (0.735 – 0.750)	0.019
Mosaic	3.6% (-0.078 – 0.149)	4.8% 90.045 – 0.052)	0.462