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IVF OUTCOMES IN BRCA CARRIERS WITH AND WITHOUT ADDITION OF LETROZOLE TO STIMULATION

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OBJECTIVE:
Women with BRCA 1/2 mutations are commonly referred to reproductive endocrinologists to discuss fertility preservation options prior to ovarian and breast cancer risk reducing surgery. Researchers remain divided about whether BRCA carriers might be predisposed to decreased ovarian reserve and accelerated ovarian aging compared to noncarriers, and debate optimal stimulation dosage and protocols.[1] The aromatase inhibitor letrozole is commonly used during controlled ovarian stimulation (COH) of breast cancer patients to minimize circulating Estradiol levels, but it is unclear whether its use negatively affects stimulation response, fertilization, and embryo quality. Our study aims to evaluate IVF outcomes in BRCA carriers who include or do not include Letrozole during stimulation.

MATERIALS AND METHODS:
The study included BRCA mutation carriers without a diagnosis of cancer who underwent COH from March 2009 to April 2021. Study groups were segregated by stimulation type (Group A: IVF cycles with Letrozole; Group B: IVF cycles without Letrozole). Basic demographic and cycle characteristics were compared between the groups. Both cohorts included cycles in which preimplantation genetic testing for aneuploidy (PGT-A) and/or monogenic/single gene defects (PGT-M) via Next Generation Sequencing for both BRCA and aneuploidy screening was performed. Data was analyzed using student's t-test, chi-square and logistic regression.

RESULTS:
A total of 72 IVF cycles for embryo cryopreservation (n=59) and egg freezing (n = 13) were included. Patients in which Letrozole was included during stimulation (n=22) were similar to group B (n=50) in baseline characteristics. Study groups were stimulated with an equivalent cumulative gonadotropin dose and had similar oocyte yield, number of mature oocytes, fertilization rate and number of embryos biopsied. 78 embryos from Group A and 219 embryos from Group B underwent PGT-A, which demonstrated equivalent rates of embryonic aneuploidy. 46 embryos from Group A and 47 embryos from Group B underwent PGT-M for BRCA, which demonstrated equivalent number of BRCA-free embryos. On multivariate logistic regression, after adjusting for age, BMI, D3 FSH, D3 E2, Gravidy, Parity, Gonadotropin Cumulative Dose, BAFC, and AMH, there was no association with use of Letrozole and lower number of oocytes retrieved (OR 1.41 (95% CI 0.47-4.19), lower number of mature oocytes (OR 0.951 95% CI 0.31-2.90), and lower number of usable euploid, BRCA embryos (1.76 95% CI 0.25-12.66).

CONCLUSIONS:
Women with BRCA 1/2 mutations are increasingly undergoing prophylactic fertility preservation. Our study is the first to demonstrate that BRCA carriers who undergo IVF stimulation with or without Letrozole experience similar clinical outcomes. As more of these women utilize PGT-M in order to

eliminate the BRCA mutation from their future offspring, they can also be comforted that stimulation with Letrozole doesn't compromise reproductive potential through their IVF cycle.

IMPACT STATEMENT:
COH that includes Letrozole for BRCA carriers to suppress the rise in E2 does not adversely impact clinical outcomes.

REFERENCES:
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