OVARIAN STIMULATION OUTCOMES IN WOMEN WITH PATHOGENIC VARIANTS IN HEREDITARY GYNECOLOGICAL CANCER GENES

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Background
Previous studies suggest that disease-causing variants in the BRCA1/2 pathway alter ovarian function by impairing DNA repair, leading to oocyte apoptosis, early ovarian aging and increased risk of diminished ovarian reserve (1, 2). The effects of other hereditary cancer gene variants are not well studied. We hypothesize that patients with pathogenic germline variants in the genes associated with an increased risk of ovarian, endometrial or breast cancers may have reduced oocyte yield and maturation rates during controlled ovarian stimulation. Understanding this possible association is crucial for improving patient counseling and fertility outcomes in women at risk.

Objective
To compare oocyte yield, maturation rates, dose of gonadotropins and length of the stimulation for in vitro fertilization cycle (IVF) in women with pathogenic variants of hereditary gynecological cancer syndromes with Anti-Mullerian hormone (AMH) - matched women undergoing elective oocyte cryopreservation.

Materials/Methods
This was a retrospective cohort study conducted in a single academic institution. Fourteen patients with pathogenic variants in genes associated with increased risk of breast, ovarian and endometrial cancer (Cases) who underwent controlled ovarian stimulation were included in the analysis. The genes studied include: *BRCA1, BRCA2, BRIP1, PALB2, MLH1, MSH2, PMS2, CHEK2, and TP53*. These patients were AMH-matched on a ratio of 2:1 with 28 women who completed elective oocyte cryopreservation (Controls). The selection of controls was performed maintaining the same age range in both groups. The outcomes of interest included: total number of oocytes retrieved, number of mature oocytes (MIIs), total dose of gonadotropins and length of stimulation of the first IVF cycle. A sub-group analysis compared women with pathogenic variants and history of cancer (Cancer) to women with pathogenic variants without history of cancer (No cancer). Data were analyzed using Wilcoxon rank sum tests with a significance level of alpha=0.05. Analyses were conducted in R version 4.4.1.
Results
A higher dose of gonadotropin was needed for patients with pathogenic variants in the genes studied compared to controls ($p = 0.024$; Table 1). While no statistically significant difference

was observed in the total number of oocytes retrieved, patients with pathogenic variants required around 1000 units of gonadotropins more to obtain only half of the number of oocytes obtained by controls (median 10 and 19 respectively for cases and controls, p= 0.45). Oocyte maturation rate and total days of stimulation were similar among groups. No difference was observed in the subgroup analysis of patients with pathogenic variant and history of cancer when compared to those without history of cancer (Table 2).

Conclusion:
Our study suggests that patients with pathogenic variants in hereditary gynecological cancer genes may require significantly higher gonadotropin dose to achieve oocyte yields comparable to AMH-matched controls. This highlights the need for individualized stimulation protocols to optimize fertility outcomes in this population. Larger studies to confirm these findings and to evaluate developmental competence of the retrieved oocytes are needed.

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References:
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Tables:

Table 1. Ovarian stimulation outcomes among women with pathogenic germline variants in genes associated with increased risk of gynecological cancer (Cases) compared to women who completed elective oocyte cryopreservation (Controls)

	Cases (N = 14) Median (Q1, Q3)	**Controls** (N = 28) Median (Q1, Q3)	**p-value**
Age	37 (32, 39)	33 (31, 35)	0.064
AMH	1.97 (1.10, 2.78)	2.60 (1.30, 4.75)	0.304
AFC	10 (7, 11)	11 (8, 22)	0.316
Total days of stimulation	10 (10, 12)	10 (9, 11)	0.103
Total dose of gonadotropins	4,050 (3,600, 4,838)	3,063 (2,250, 4,050)	0.024
Total number of oocyte retrieved	10 (7, 15)	19 (7, 25)	0.446
Total number of MIIs	8 (6, 11)	12 (6, 19)	0.323

Table 2.Ovarian stimulation outcomes among women with pathogenic germline variants and a diagnosis of cancer (Cancer) compared to women with pathogenic germline variants without personal history of cancer (No cancer)

	Cancer, N = 8 Median (Q1, Q3)	**No Cancer**, N = 6 Median (Q1, Q3)	**p-value**
Age	37 (35, 40)	35 (31, 38)	0.603
AMH	1.97 (1.27, 3.41)	1.77 (0.74, 2.53)	0.366
AFC	10 (7, 13)	11 (6, 11)	0.744
Total days of stimulation	11 (10, 12)	10 (10, 11)	0.300
Total dose of gonadotropins	4,275 (3,488, 5,063)	4,050 (3,713, 4,388)	0.795
Total number of oocyte retrieved	9 (8, 25)	12 (8, 13)	0.796
Total number of MIIs	9 (7, 13)	7 (6, 10)	0.604