

Significant Post-Chemotherapy Decrease of Ovarian Reserve in Iranian Women With Breast Cancer

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Abstract- Fertility preservation counseling has a high priority in young breast cancer (BC) patients. Cytotoxic chemicals used for chemotherapy in these patients increased the risk of premature ovarian failure. This study evaluated the anti-mullerian hormone (AMH) level at the time of diagnosis and within a month after the end of chemotherapy, while predicting the time of the return of ovarian function in BC cases (n=46) younger than 46 years for the first time in Iran. Cases were selected from those attending the breast oncology clinic of the two hospitals with a newly diagnosed in situ or invasive BC. The present study results showed AMH levels were significantly decreased in almost all women within a month after chemotherapy. It seems that the need for fertility preservation depends on patient age and baseline AMH level, but counseling should be offered by the clinician in young breast cancer patients.

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Introduction

Fertility preservation in young women with breast cancer is a key component of cancer care and will improve the quality of life. Anti-mullerian hormone (AMH), with only minor fluctuations in serum concentrations during the normal menstrual cycle, is a known sensitive biomarker for fertility and ovarian reserve (1). Since breast cancer patients in Iran are relatively younger than western countries (2), evaluation of fertility and ovarian reserve before any cytotoxic treatment and fertility preservation counseling and related procedures have a high priority in those who have not yet completed their family planning.

There is plenty of evidence about the increased risk of premature ovarian failure due to cytotoxic chemicals used for chemotherapy in breast cancer (3). The majority of studies have evaluated the effect of some variables such as older age, hormonal profile, and menstrual status to predict future fertility potential after treatment (4,5).

Based on our knowledge, there is not any published study related to ovarian reserve in breast cancer patients in Iran. Therefore, the objective of our study was to evaluate the AMH level at the time of diagnosis and within a month after the end of chemotherapy while predicting the time of the return of ovarian function in these patients.

Materials and Methods

This study was approved by the ethics committee of Tehran University of Medical Sciences (IR.TUMS.VCR.REC.1397.242), and it was performed in two university hospitals of Tehran, the capital city of Iran. Written informed consent was obtained from all participants prior to blood sample collection. Patients were enrolled from July 2018 to February 2020. Breast cancer cases were selected from women attending the breast oncology clinic of the two hospitals with a newly diagnosed in situ or invasive breast cancer and had not

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yet received any anticancer treatment, but were candidates of chemotherapy for the management of their disease. All participants (n=46) were younger than 46-year-old. A trained interviewer gathered individual information about demographics, reproductive and menstrual history, and breast cancer-related information by in person-interview. Hospital nurses collected a 5 ml blood sample before any treatment was started for the patient. Samples were stored at room temperature and transferred to Arash Women's hospital laboratory within two hours. AMH was measured using the AMH enzyme-linked immunosorbent assay kit (Beckman Coulter, AMH gene II assay, Brea, CA, USA) with a limit of detection (LOD) of 0.08 ng/ml. Intra-assay and inter-assay variations were 7.7 %. A second sample was collected, transferred, and tested for AMH within a month after the end of chemotherapy.

SPSS software (version 20, SPSS, Inc, IL, USA) was used for all statistical analyses. Results were presented as mean±standard deviation (SD) for continuous variables and frequency for categorical variables. Correlation between age and AMH levels was performed with Pearson correlation or Spearman based on the normality of data.

According to the scoring system suggested by Su *et al.*, (6), we calculated a prognostic score based on age <40 years, AMH >0.7 ng/mL, and body mass index ≥ 25

kg/m² to estimate the timing of the return of ovarian function. One point was assigned for each factor. Considering the total score, we estimated the time of the return of ovarian function as measured by the menstrual pattern.

Results

Overall, 46 cases were entered into the study. The mean age of participants was 35.85±4.58 (range: 25-45-year-old), and 36 patients (78.3%) were younger than 40-year-old. The mean level of AMH before treatment was 3.20±2.84 (Median=2.28) and 0.26±0.70 ng/mL (Median=0.1) within a month after chemotherapy. AMH level at the time of diagnosis was distributed normally (Kolmogorov–Smirnov test, $P=0.15$), but it was not normal after chemotherapy (KS test, $P<0.001$). While a strong negative correlation between AMH at the time of diagnosis and age ($r= -0.48$, $P=0.01$) was shown by Pearson correlation, we did not find a correlation between AMH after chemotherapy and age. Our results showed that AMH level was significantly decreased, and 97.8% (n=45) of women had AMH level less than 0.5 ng/mL; only one patient had an AMH level higher than 1 ng/mL after chemotherapy (Table 1).

Table 1. AMH level categories at the time of diagnosis and within a month after chemotherapy (n = 46)

AMH category (ng/mL)	At the time of diagnosis	After chemotherapy
<0.5	7 (15.2)	45 (97.8)
0.5-1	9 (19.6)	1 (2.2)
1.1-3.4	13 (28.3)	0
≥ 3.5	17 (37)	0

AMH: Anti-mullerian hormone

We calculated the probable time of the return of ovarian function, according to Su *et al.*, score (6). Only one woman (2.2%) received a zero score. Score 1, 2, and

3 were obtained in 9 (19.6%), 19 (41.3%), and 17 (37%) women, respectively. The estimated time of the return of ovarian function is demonstrated in Table 2.

Table 2. Prognostic score to estimate the time of the return of ovarian function

Score	Number (%)	Time to return of ovarian function, day (6)		
		25%	50%	75%
0	1 (2.2)	221	-	-
1	9 (19.6)	189	325	570
2	19 (41.3)	106	163	246
3	17 (37)	96	118	160

The total score was assigned after adding one point score for each of the following items: age less than 40 years, AMH level higher than 0.7 ng/mL, and BMI ≥ 25 kg/m²

Discussion

The results of the present study showed that AMH levels were significantly decreased in almost all women within a month after chemotherapy, and post-chemotherapy AMH level was not affected by age.

Several studies reported a very low level of AMH within a month after chemotherapy (7,8). Yu *et al.*, showed that the serum concentration of AMH decreased significantly at 6 weeks after chemotherapy and remained suppressed for 52 weeks (median 0.05 ng/mL) (7). Another study by Henry and colleagues evaluated the effect of chemotherapy on AMH level in breast cancer patients and reported that baseline means the level of AMH (1.95 ± 2.17 ng/mL) significantly decreased to a mean of less than 0.16 after one month of chemotherapy (8). Based on their results, although the AMH level increased after one-year post-chemotherapy (mean; 0.23 ± 0.22), it was still a very low level of ovarian reserve (8). The results of the above-mentioned studies related to AMH level after chemotherapy are consistent with our study.

As explained in the method section, Su *et al.*, the study has predicted the time of the return of an ovarian function (menstrual cycles) according to age, AMH level at the time of diagnosis, and BMI. They generated a novel formula to help clinicians decide for fertility preservation in breast cancer patients before cytotoxic treatment (6). In our work, we estimated the time of ovarian return function by this method. According to data illustrated in Table 2, 75% of our patients' menstrual cycle would return 5 to 19 months after chemotherapy. Since our study will follow patients until two years after chemotherapy, we will report the exact time of the return of the menstrual cycle and the AMH level after two years in our Iranian population and compare our results with the above estimated time.

Given the importance of the issue, we have decided to publish these results before the 2-year follow-up in order to provide guidance to Iranian physicians. Firstly, they should know that almost all patients lose their ovarian function after chemotherapy, which endorses sharing the point with women who desire to have children in the future before further treatment. Secondly, in order to offer fertility preservation to breast cancer patients, they could estimate the time of the return of ovarian function considering age, AMH level, and BMI.

A recent study showed that breast cancer patients with *BRCA* mutation have significantly lower serum AMH levels and they recommended that fertility preservation should be considered more aggressively in

young breast cancer patients with *BRCA* mutation (9). In this study, the genetic evaluation was not performed due to the lack of budget. Therefore, we think further studies are needed to find clinical, biochemical, and genetic variables related to changes in AMH levels in breast cancer patients.

Furthermore, temporary ovarian suppression with GnRH analogs during chemotherapy is a potential strategy to prevent premature ovarian failure (POF) in young patients, and the efficacy of its usage before and during chemotherapy, including a resumption of menstrual cycles and spontaneous pregnancy, was confirmed by a meta-analysis study (10). However, because of lacking data, included studies were unable to compare the results between subtypes of breast cancer or different chemotherapy regimens.

Based on the present study results and previous studies, it seems that the need for fertility preservation depends on patient age and baseline AMH level, but counseling should be offered by the clinician in young breast cancer patients. However, it could be optional because we expect the menstrual pattern and ovarian function of young patients will return in less than two years.

Long-term data, as well as the final results of our ongoing study, will reveal the time of the return of ovarian function in our population.

In conclusion, the impact of chemotherapy on ovarian function should be accurately assessed by breast oncologists, and gynecologists and the estimated risk of chemo-induced amenorrhea and infertility has to be taken into account.

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