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Research Article

Fertility Desire and Protection Practices Among Turkish Young Breast Cancer Patients Treated with Chemotherapy

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Abstract

Objectives: This study aims to reflect the oncofertility practice in Turkey as a developing country, by investigating young breast cancer patients' fertilization preservation attitudes and their post-treatment fertility status.

Methods: Young breast cancer patients(<42 years) examined for breast cancer follow-up at the medical oncology outpatient clinic were consecutively included in the study. Patients with metastatic, infertile, or no menstrual cycle at the time of diagnosis and women who were less than 3 years from their last chemotherapy cycle were excluded. A questionnaire on the desire for childbearing in the future, the fertility preservation preferences at the time of diagnosis, reproductive history was surveyed with patients.

Results: 123 patients were enrolled in the study. 23.5% of the patients reported that they had a desire to give birth in the future at the time of diagnosis. For fertility preservation; 6 patients used embryo or oocyte cryopreservation, and 16 patients used LHRHa during chemotherapy.

Nulliparous patients were more likely than others who had at least one child to pursue fertility preservation (p=0.001) and to be interested in having children in the future (p<0.001).

Conclusion: This study revealed that oncofertility practices should be encouraged to improve the quality of life of survivors along with cancer treatment in developing countries. Even with fertility preservation, the chances of a successful pregnancy are significantly low. Physicians should offer protection options to all patients regardless of their previous childbearing status, and fertilization counseling should also be discussed during all the post-treatment visits as well as pre-treatment settings.

Keywords: Chemotherapy, oncofertility, fertility preservation, young breast cancer, pregnancy, childbearing

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Breast cancer is the most frequently diagnosed type of cancer worldwide and the leading cause of cancer death in women. In the United States, 281,550 women died from breast cancer in 2021.[1] Breast cancer at a young age has been linked to poor outcomes.[2-3] Recent advances in breast cancer treatments have resulted in a reduction in breast cancer mortality regardless of age and tumor characteristics.[4] However, Cytotoxic chemotherapy can affect fertility by causing premature ovarian failure.[5] Chemotherapy damages developing follicles or primordial follicles by directly causing DNA damage or triggering indirect intracellular signaling pathways.[6,7] Fertility is mainly related to ovarian reserve as well as chemotherapy type, duration, dose, and combination treatments.[8] Although age is the main determinant of ovarian reserve, genetic and lifestyle factors (stress, parity, basal metabolic index, and smoking)have also an effect.[9]

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With the rise in the number of survivors following breast cancer treatments; issues such as quality of life, having a job, and childbearing in the future become important for the remaining long-term lives of the survivors. Many women, especially those who do not have a child yet, desire childbearing in the future.[10] Given the rising trend in delaying childbearing and the rising number of childless patients at the time of diagnosis, demand for information on post-treatment fertility potential and the feasibility and safety of pregnancy is expected to increase. American Society of Clinical Oncology guidelines recommend discussing fertility issues with all cancer patients of reproductive age before starting chemotherapy.[11] Fertilization preservation(FP) requires individualization, taking into account the patient's desire for future pregnancy, the planned treatment, the patient's age, and the partnership status or financial characteristics of patients.[12,13] Cryopreservation of embryos or gametes is the accepted method for fertility preservation.[11,14,15] Consultation for fertility preservation at initial diagnosis is appropriate to accelerate the options for alternative fertility preservation techniques, including Controlled Ovarian Stimulation (COS) and embryo cryopreservation or oocyte retrieval. It is recommended that women with reproductive potential desiring fertility preservation should be referred rapidly to a reproductive endocrinologist.[16]

This study aims to investigate the fertilization preservation attitudes and childbearing decisions of young breast cancer patients before chemotherapy and their fertility status after treatment.

Methods

Study Population

This retrospective study included female patients aged ≤42 years with a histologically proven diagnosis of invasive breast cancer treated with chemotherapy for curative intent between January 2012 and December 2017. To be included in the study, at least three years must have passed over the last chemotherapy cycle. Patients with metastatic, recurrent disease, ductal carcinoma in situ, and a proven infertility diagnosis or without surgery for BC (breast cancer) were excluded from the study as well as patients who received previous cancer treatment. The study was approved by the Tekirdag Namik Kemal University ethics committee under the Helsinki declaration, and informed consent was obtained from all participants.

Data Collection and Management

Patients' demographic information, treatment, and breast cancer outcome data were obtained from the hospital electronic record system. A questionnaire was surveyed by the same physician in the research team to each patient face-to-face with questions about fertilization requests, reproductive history, fertilization preservation method preferences (if present), post-treatment fertility status, and fertilization issues.

Study Questionnaire

The Study Questionnaire was developed by the research team in accordance with the literature to evaluate breast cancer fertilization information. The questionnaire was comprised of 16 questions, including 3 questions on demographic information, 3 questions on study eligibility, 4 questions on fertilization preferences, 2 questions on reproductive history, and 4 questions on the menstrual cycles after treatment. Most of the questions require simple yes/no answers. In questions with multiple answers, the participants were instructed to select any/all appropriate responses.

Statistical Analysis

The Fisher exact test and the Mantel–Haenszel chi-square test were used to evaluate the relationships between fertility desire at diagnosis, having children before diagnosis, age, stage, and fertility preservation. All p values less than 0.05 were considered significant. SPSS version 26.0 (SPSS Inc., Chicago, Ill) was used for all statistical analyses. Continuous variables are illustrated using the median and range. Categorical variables were summarized using frequency and percentage.

Results

We included 123 female patients in this study. The median age was 37 years (24–42). While one-third of patients were <35 years old, 27 patients were older than 40 years. The majority of the patients(80.5%) had an educational level of high school or below education degree. 82% of the tumors were estrogen/progesterone-receptor(ER/PR) positive whereas 14 % were triple-negative. Five patients were ER/PR negative and HER2 positive tumors. The demographic information of the patients and the proportions of patients receiving adjuvant HER2-directed and/or hormone therapy are summarized in Table 1.

Future Fertility Considerations and Preference

111 (90.2%) of the patients had at least one child at the time of diagnosis of breast cancer. 29(23.5%) out of 123 patients stated that they desire to have children in the future when they were diagnosed. Of 29 patients, 9 were nulliparous, 11 had one child, while the remaining stated that they had 2 or more children. For fertilization protection; 5 patients used embryo cryopreservation, 1 patient

Table 1. Patients' Clinicopathologic Features (n=123)

Characteristic	n	%
Age at diagnosis		
Median age	37	24-42
<35 (Very Young Adult)	41	33
35-42	82	67
Education		
Elemantary school	57	46
High School	42	34
Colloge or higher	24	20
Time since diagnosis(years)		
3-5	34	27
5-10	70	56
>10	19	17
Hormone/HER2 reseptor statıus		
ER/PR+ and/or HER2+	101	82
Triple negative	17	14
ER/PR- and HER2+	5	4
Stage		
1-2	68	55
3	25	20
Missing	30	25
Chemotherapy		
Adjuvant	22	18
Neoadjuvant	101	82
HER2 Directed Therapy		
Yes	27	21
No	96	79
Endocrine Therapy		
Yes	101	82
Tamoxifen only	37	30
Tamoxifen + OFS	48	39
AI+OFS	16	13
No	23	18

HER-2, Human epidermal growth factor receptor 2; ER, estrogen receptor; PR, Progesterone receptor; AI: Aromatase inhibitör; OFS: Ovarian Function Suppression.

used oocyte cryopreservation, and 16 (13%) patients used LHRHa(Luteinizing Hormone-Releasing Hormone analog) during chemotherapy (Table 2). Nulliparous patients were more likely than others who had at least one child to pursue fertility preservation [7/12(58%) vs. 14/111(11%) p=0.001] and to be interested in having children in the future [9/12(75%) vs 20/111(18%) p<0.001]. In addition, very young patients(<35 years old) compared to those aged ≥35 years [15/41(36%) vs. 6/82(7%) p<0.001] and patients who had the desire for pregnancy in the future compared to those who had not [12/29(41%) vs. 9/94(9%) p<0.001] were more likely to pursue Fertility Preservation (Table 3).

Table 2. Questions About Fertility Preferences & Preservation

Questions	n (%)
Children at time of BC Diagnosis	
0	12 (9.8)
≥1	111 (90.2)
Desire for Future Childbearing?	
Yes	29 (23)
No	94 (77)
Reason for not being Interested in Future childbearing?	
Already have children/a child	74 (78)
Fear of recurrence	8 (8.51)
Was not married	7 (7.44)
Others	5 (5.31)
Fertility Preservation Before the Treatment?	
Freeze eggs	1 (0.81)
Freeze embryos	5 (4.08)
Goserelin during chemotherapy	16 (13)
None	102 (82.1)

BC; Breast Cancer.

Table 3. Fertility Preservation and Patients-Related Features

Characteristic	Fertility Preservation		p
	No (n, %)	Yes (n, %)	
Age			
<35 years	26 (21.1)	15 (12.2)	**<0.001**
≥35	76 (61.8)	6 (4.9)	
Stage			
1-2	58 (47.6)	10 (8.1)	1.000
3	21 (17.1)	4 (3.2)	
Education			
College	53 (43.1)	13 (10.5)	0.405
Primary or High School	49 (39.9)	8 (6.5)	
Having a Child Before Diagnosis			
Yes	97 (78.9)	14 (11.4)	**0.001**
No	5 (411)	7 (5.7)	
Fertility Desire at Diagnosis			
Yes	17 (13.8)	12 (9.8)	**<0.001**
No	85 (69.1)	9 (7.3)	
Hormone Reseptor Status			
Positive	87 (70.7)	14 (11.4)	0.059
Negative	15 (12.2)	7 (5.7)	

s: Significant values are indicated in bold.

Reproductive Health

96 (78%)patients developed amenorrhea with chemotherapy. Out of 96 patients, 21(17.1%) patients had no menstrual periods again, while 35 women were continuing on

adjuvant LHRHa at the time of the survey. The remaining 30 (24.4%) patients regained their menstrual cycle in a median of 6 months. Among the 30 patients, 17 had regular menstrual cycles, whereas 13 had irregular menstruation (Fig. 1). Among the 37 patients who received only adjuvant tamoxifen hormone therapy, 10 (27%) returned regular periods, while 27 (73%) had irregular or no menstruation.

Subsequent Births

Six of the patients included in the study gave birth, and one patient's pregnancy ended in miscarriage. Of the 21 Patients desiring future pregnancy at the time of diagnosis and pursuing FP and/or using LHRHa during chemotherapy, 2 patients gave birth. Among the patients not interested in future pregnancy or fertility preservation, 5 patients conceived spontaneously (Fig. 2).

Discussion

In our study, we found the fertilization preservation rate to be approximately 17% in young breast cancer patients most of whom had at least one child and a relatively little desire for childbearing in the future. Nearly 5% of the entire patient population had a child after breast cancer treatment. The fact that a small number of patients have a child after breast cancer treatment is a true reflection of real-life problems such as cost-effectiveness, treatment concerns, partnerships, etc. Similarly, Partridge, Ann H et al reported that 9% of the 384

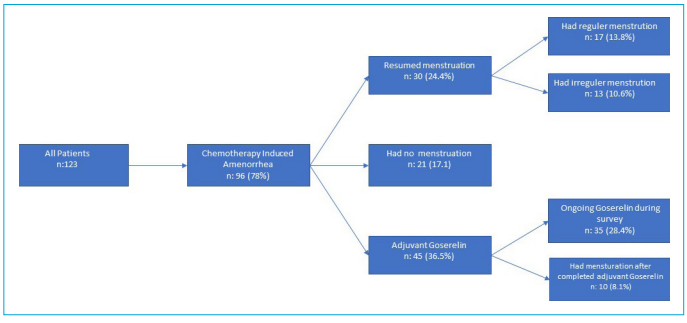

Figure 1. Treatment-Related Reproductive Health of the Patients.

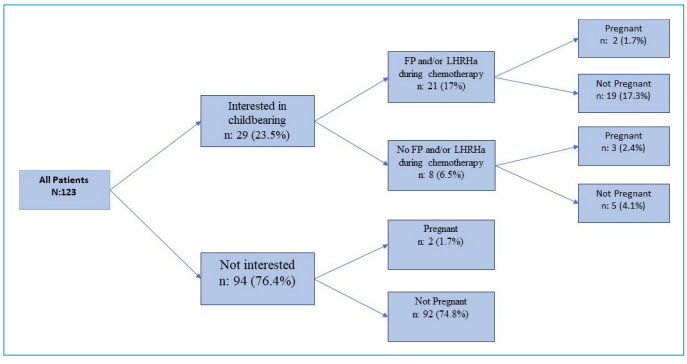

Figure 2. Future Fertility Considerations & Preservation Preferences, and Outcomes.

breast cancer patients treated with chemotherapy had offspring after chemotherapy.[17] In a study by Lee, Sunyoung, et al., of the 326 patients undergoing chemotherapy for breast cancer, 41% of the patients regained their cycles, and only 4 of these patients were able to conceive subsequently.[18] These findings demonstrated that childbearing should be dealt with at all treatment stages in terms of improving the quality of life of breast cancer survivors.

Young breast cancer patients may not prioritize fertilization preservation due to concerns about breast cancer treatments and the possible effects on the prognosis of the disease caused by delays related to fertilization preservation processes.[19] Whereas, the fertility preservation process is considered not to be associated with recurrence of breast cancer and significant delay in initiation of treatment.[20,21] The low rate of fertilization preservation may be related to inadequate information about the effects of chemotherapy on fertility, concern about the impact of possible pregnancy on breast cancer prognosis, patients' socioeconomic status, concern for the delay in treatment if FP is pursued, limited interviews during visits or lack of knowledge of physician.[22,23] In addition, the countries and regions where the patients live have an impact on this situation.[24,25] In developed countries, the tendency to postpone reproduction continues to rise.[26] Thus, later childbearing increases the significance of fertility conservation strategies. We observe that young breast cancer patients in developed countries undergo higher fertility preservation prior to their cancer treatment. In a study that included mostly nulliparous women (74.9%) from Scotland, it was reported that 51.5% of the patients had pursued a fertilization preservation strategy.[27] In another study of young patients with breast cancer in the United States, Letourneau, Joseph M et al. reported that 63% of the patients used the fertilization preservation strategy.[21] However, the fertility preservation rate or access differs in developing countries.[28] Studies showed the lack of knowledge on oncofertility and the obstacles to the practices of fertility preservation in developing countries unlike the developed countries.[29,30] It was reported that only 16 successful oocyte-egg cryopreservation out of 146 breast cancer patients under 42 years old from Iran.[31] During a 4-year-long prospective study of breast cancer patients younger than 40 years of age in Mexico, 12% of patients pursued fertility preservation.[32] Consistent with this, we showed that fertility preservation strategies were pursued by a small number of patients in our study. The causes of the low rate of fertilization protection may be related the obstacles such as financial limitations, lack of specialists or reproductive units, patients' sociocultural features, or legal barriers related to different methods of parenthood (surrogacy, adoption by the homosexual partnership, etc.) specific in developing countries. However, we consider that

the most important reason for the low rate of fertilization protection is that 77% of the patients had no desire for a future pregnancy.

Studies on fertilization desire in young breast cancer patients have shown that nulliparous patients have a higher tendency for childbearing and fertilization protection.[33,34] McCray, Devina KS et al reported that 26% of 303 young patients with breast cancer had a fertility desire in the future. They also reported that having fertility desire was associated with younger patients' age and having fewer children at the time of diagnosis.[35] In a study, Goldfarb, Shari B et al showed that 50% of the women were not interested in having children in the future, and they reported women who had never been pregnant were significantly more likely to be interested in having children in the future.[36] In accordance with this, our study revealed that patients who had no child were more likely to desire for having a child in the future than women who had at least one child. Though, patients' concerns, such as a shorter life expectancy or feelings of guilt towards their possible future children, should also be kept in mind when assessing their desire to have a child in future.

Fertility rates among young breast cancer survivors have historically been less likely than their healthy counterparts, however, they may have healthy children during adjuvant treatments even if they did not pursue fertilization. As in our study, whether to pursue FP or not in terms of pregnancy outcomes had similar results. Although this could be attributed to the low number of FP in our study, many studies in the literature showed that pregnancy rates after chemotherapy are low even if FP is performed.[35-37] Therefore, instead of limiting fertility discussions to just before treatment, it may be appropriate to discuss fertilization issues with patients continuously throughout adjuvant treatments.

Administration of GnRHa with chemotherapy is considered a modality for gonadal protection.[38] In our study, one of 16 (13%) patients using LHRH agonists during chemotherapy gave birth without assisted reproductive technology. However, the effectiveness of using LHRHa as a "fertility preservation" method is controversial.[39] In a study that included 227 patients, Leonard, R C F et al reported that patients using goserelin for ovarian protection, particularly for women less than 40 years of age, were less likely to have a premature ovarian failure.[40] Therefore, GnRH may be offered to patients to reduce chemotherapy-induced ovarian failure where proven fertility preservation methods are not feasible.[39]

The incidence of chemotherapy-induced amenorrhea(CIA) is reported to be up to 90%, depending on the patient population and follow-up period.[41,43] In a study of young breast cancer patients, most of whom were over the age of 40, Tiong V et al. reported that 93.1% of the patients had developed chemotherapy-associated amenorrhea. Of these patients who developed amenorrhea, 24.6% regained their menstrual cycle at a median of 7.86 months.[44] Tham, Yee-Lu et al reported the rate of chemotherapy-induced amenorrhea as 60% in their study, and they reported that 40% of women aged <40 years with CIA lasting for more than 6 months had resumed their cycles. They also found that the addition of taxane to the anthracycline plus cyclophosphamide regimen and being over 40 years of age were independently associated with CIA.[45] In our study, 78% of patients developed amenorrhoea with chemotherapy. 41% of patients with CIA regained cycles again in a median of 6 months.

Absence of menstruation while taking tamoxifen does not always indicate impaired fertilization. Reported rates of amenorrhea may incorrectly overestimate the actual risk of ovarian dysfunction associated with tamoxifen use. Ting AY et al. reported that tamoxifen use was not related to CIA in their study.[46] It has been reported that tamoxifen does not increase the risk of permanent ovarian dysfunction, but due to its effect, it may disrupt the menstrual cycle.[47] On the contrary, Partridge et al claimed that it may impair fertility by showing lower serum AMH levels in women on tamoxifen.[48] In our study, 69% of patients received or continue to receive tamoxifen in their adjuvant treatment setting. Given the mentioned modest impact of adjuvant tamoxifen treatments on fertility, few patients interrupted endocrine therapy and attempted to have a child in our study.

The main limitation of our study is the retrospective design and the fact that we could not evaluate the fertilization status of breast cancer survivors with a gold standard method (serum AMH, follicle count with USG, etc.). In addition, surveying patients at least 3 years after diagnosis, therefore, is another limitation as some patients might not precisely recall their attitudes towards fertility. But at the same time, the strength of the study is that it shows real-life data on patients who have had enough time to have a child for at least 3 years but choose not to do so.

In conclusion, in resource-limited countries such as Turkey, preservation strategies are not easily available and probably not affordable for most patients.[49] It is extremely important to establish a multidisciplinary national guideline for oncofertility that enables teams to collaborate. Physicians should inform all young patients of the risk of ovarian failure and offer protection options regardless of their previous childbearing status. Fertilization counseling should also be discussed during the post-treatment visits and consultations should also be carried out during the follow-up period.

Disclosures

Ethics Committee Approval: The present study was performed in line with the principles of the Declaration of Helsinki. The Tekirdag Namik Kemal University Ethics Committee granted formal approval to this study (approval no: 2021.16.01.16 on January 26th, 2021).

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