Journal of Obstetrics, Gynecology and Cancer Research | ISSN: 2476-5848

# Preserving Fertility and Its Outcomes in Iranian Women with Cancer: A Longitudinal Cohort Study

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**Article Info**

10.30699/jogcr.8.5.446

**Received:** 2022/11/11;
**Accepted:** 2023/01/19;
**Published Online:** 09 Sep 2023;

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**ABSTRACT**

**Background & Objective:** Preserving fertility in women with cancer before therapeutic interventions is very important. This study was evaluating the 8 years' experience of an onco-fertility center from 2013 to 2020 on fertility preservation and its outcomes in female cancer survivors.

**Materials & Methods:** Participants were females with an approved cancer diagnosis of reproductive ages that were referred for fertility preservation. After proper counseling by an expert team, the final decision on the fertility preservation method was made based on the patient's condition and survival expectation. The primary goal was to collect data about the fertility, clinical and survival outcomes of these women and pregnancy rate as a secondary objective that were compared between cancer types.

**Results:** Totally 337 participants were recruited with a mean±SD age of 30.7±6.6 years. Gynecological cancers accounted for 166 (49.3%) of all cases followed by breast (107 (31.8%)) and other cancers (64 (19.0%)) respectively. Of those, 144 (42.7%) cases entered into the ovulation induction cycle and the others did not continue due to lack of correct information and late referral, and inability to postpone treatment as the major reasons. Comparing between 3 groups (gynecological, breast and other cancers), a higher rate of pregnancy otherwise not statistically different was detected in gynecological cancer survivors. In the breast cancer survivors, the chance of oocyte retrieval and fertility was not lower than in other cancers.

**Conclusion:** Many patients and even their therapists are unfamiliar with the methods of fertility preservation, and when they consider it, the golden time is usually passed. Therefore, having a good consultation with the survivors and patient education may be the most important issue that led to a timely referral for preserving fertility in cancer patients.

**Keywords:** Fertility Preservation, Breast Cancer, Gynecological Cancers, Ovarian Reserve, Ovulation Induction, Quality of life



## Introduction

Cancer is considered a leading cause of morbidity and mortality at reproductive age. It is estimated that 15% of the cancers in women occur between 15-45 years old (1). Over recent years, advances in the diagnosis and treatment of cancer have improved survival rates (2). Otherwise, the cytotoxic effects of chemotherapy and radiotherapy may have impressed women's reproductive system, and decreased the chance of fertility (3). Alkylating drugs, whole-body radiation and radiotherapy below the diaphragm have the utmost risk (4) that may lead to premature ovarian insufficiency by a decrease in ovarian follicles number, ovarian stromal fibrosis and vascular injury (5). In gynecological cancers in addition to such adjuvant therapy, the surgeries in the reproductive system may affect future fertility (6). Furthermore, loss of reproductive potential after cancer treatment has a harmful impression on the quality of life (QOL) in the survivors (7).

Oncofertility is a relatively new concept, including both oncology and reproductive health for cancer patients (8). In this way, women with cancers in reproductive age might conceive without any significant impact in oncologic outcomes (9). Near 70-75% of the young cancer survivors look for parenthood (6). It is being noted that a variety of factors such as economic status, short survival, religious and moral

attitudes, complicate deciding on fertility preservation (10).

A proper consultation about preserving fertility at the time of cancer diagnosis occurs less frequently (2). It is recommended to refer these patients to an appropriate reproductive specialist as early as possible (3). Even with the increasing number of patients receiving counseling over time, the number of women who could access these facilities before treatment is significantly low (5). Nevertheless, a prompt decision for fertility preservation may lead to a shorter delay in cancer's adjuvant treatment, the ability to undergo additional fertility preservation cycles, an increase in oocyte yields, and a significant increase in cryopreserved embryos (11).

The common options for fertility preservation are the banking of either oocytes or embryos for further use that need at least 2 weeks intervals (7, 12). This method involves the hyperstimulation of the ovary to induce the growth of multiple follicles (13). If a partner is not available, oocyte's cryopreservation is a valid alternative (1). Whether in women who cannot delay treatment or in prepubertal girls, ovarian tissue cryopreservation may be served as an alternative option (14).

It was believed that women exposed to ovulation induction are transiently at higher risk of breast and uterine cancer, although the overall incidence is not greater than expected (15). Indeed, in estrogen-dependent cancers, there is a concern that ovarian stimulation may increase disease recurrence (1), it is suggested that the administration of letrozole reduces estrogen flare and disease-free survival was similar in women with or without ovarian stimulation (16).

However, studies in this field have become available over the past few years but several issues remain controversial concerning the fertility preservation strategies in cancer survivors (17). Furthermore, the literature concerning the follow-up and the pregnancy results in these patients is lacking. In this study, we report the 8 years' experience of a referral oncofertility center on fertility preservation methods and their outcomes in female cancer survivors.

## Methods

### Patients and data collection

In this cohort, we analyzed the data of 337 females who were referred for fertility preservation between April 2013 and February 2020. The eligibility criteria were the participants with an approved cancer diagnosis of reproductive ages. The demographic and clinical data such as age, cancer type, infertility history, and marital statuses were collected either. After proper counseling by an expert team consisting of an infertility specialist, oncologist and a psychologist with every single participant, the final decision on fertility preservation method (ovulation induction, egg/embryo donation, ovarian tissue cryopreservation, or no service) was made based on the patient's condition, availability of the services and the clinical and lab data such as anti-Mullerian hormone (AMH), follicle stimulation hormone (FSH) and antral follicle count (AFC) that were measured in the single referral center. In oocyte retrieving cycles, the amount of gonadotropin used, the duration of ovulation induction and the number of retrieved eggs were collected either.

The primary goal was to collect data about the clinical and survival outcomes of these women, and the pregnancy rate as a secondary objective. In the participants who did not return for follow-up, a specialist called them by phone number to collect the missing data as possible.

### Ethical Approval

This study was approved by the Ethics Committee of Tehran University of Medical Sciences

(Reference number: IR.TUMS.IKHC.REC.1397.193). All participants read and signed the informed consent before the study initiation. This study was performed due to the Helsinki declaration.

### Ovulation Induction and Oocyte Retrieval Cycles

The first option was oocyte retrieval cycles and most participants had the criteria to enter the cycles, whereas a few participants were not good candidates for ovulation induction due to their old age, unsuitable lab index or disagreement of their oncologists to receiving hormones. Egg/embryo donation or ovarian cryopreservation was suggested in this population. For a few patients depending on their situation (very short survival), no service was provided.

For the patients who entered an oocyte retrieval cycle, the gonadotropin-releasing hormone (GnRH) antagonist protocol was administered by random or conventional start depending on the day of referral. In the participants referred in the first 5 days of their menstrual cycle (follicular phase), transvaginal ultrasonography (TVUS) was performed to evaluate the AFC and endometrial thickness and recombinant FSH (Gonal-F; Merck Serono) subcutaneously (with doses ranging from 150 to 300 IU/day according to their age, AFC and ovarian reservoir) began.

In breast cancer, letrozole (10 mg) was administered in combination with the standard protocol at the same time. The dose was adjusted according to the ovarian response assessed by follicular growth by TVUS daily or every other day for detecting the pattern of folliculometry and endometrial thickness. After the follicle(s) reached the size of 14 mm, 0.25 mg of GnRH antagonist (Cetrorelix; Cetrotide, Merck Serono, Italy) was added to prevent luteinizing hormone (LH) surge.

For the patients referred in the late follicular or luteal phase, the random starting of the GnRH antagonist

protocol was applied the same as the conventional start except that gonadotropin started from the day of admission.

Oocyte retrieval was performed by vaginal ultrasound-guided aspiration. Then, the oocytes were transferred to 20µL droplets of culture medium covered with mineral oil and incubated at 37ºC and 6% CO2 for two hours. Metaphase II oocytes were confirmed by the presence of two pronuclei and were cryopreserved using vitrification.

### Statistical Analysis

The statistical analysis was mainly descriptive. The variables would be summarized using mean±SD (standard deviation) or range and to test differences between groups when applicable, one-way ANOVA was used. The data were analyzed using SPSS-version 23. A P-value of less than 0.05 was considered statistically significant.

## Results

Of 337 participants who were referred for oncofertility counseling, 201 (59.6%) were married and 136 (40.4%) were single. The mean±SD age was 30.7±6.6 years (range: 12-45 years). Of all, 22 (6.5%) cases were in the adolescent age (12-19 years) and 30 (8.9%) were 40-45 years old. The total number of patients with gynecological cancer, breast cancer, and the others were 166 (49.3%), 107 (31.8%), and 64 (19.0%) respectively. The fertility options for each participant are listed in Table 1.

**Table 1. Fertility preservation techniques in the patients referred to the oncofertility center based on their cancer type**

| Fertility Preservation Technique | Gynecological cancers (%) n=166 | Breast cancer (%) n= 107 | Others (%) n= 64 |
|---|---|---|---|
| **Oocyte retrieval cycles** | 92.0 | 88.6 | 95.6 |
| **Before chemoradiation** | 86.2 | 68.6 | 53.3 |
| **After chemoradiation** | 5.8 | 20.0 | 42.3 |
| **Egg/Embryo Donation** | 2.2 | 4.3 | 4.4 |
| **Before chemoradiation** | 1.5 | 0 | 0 |
| **After chemoradiation** | 0.7 | 4.3 | 4.4 |
| **Ovarian Tissue Cryopreservation** | 2.2 | 0 | 0 |
| **Before chemoradiation** | 2.2 | 0 | 0 |
| **After chemoradiation** | 0 | 0 | 0 |
| **No Service** | 3.6 | 7.1 | 0 |
| **Before chemoradiation** | 2.9 | 4.3 | 0 |
| **After chemoradiation** | 0.7 | 2.8 | 0 |

Totally, 144 (42.7%) participants came back for follow-up. The rest of the patients did not continue for several reasons including the lack of correct information and late referral, (17.0%), not enough time for delay in surgery, or chemotherapy (14.0%), high cost of fertility preservation (11.1%), lack of belief in fertility-preserving methods (10.3%), going to another infertility center (8.8%), hymen damage in virgins or no desire to have a child in the future (6.6% each) and at last 7.4% because of unknown reason. The other minor causes were the patient's mortality or infertility of their partner and at last, 3 patients did not accept egg/embryo donation due to being eager to have their biological child.

Of these 144 patients, 79 (54.9%) had gynecological cancers, 39 (27.1%) suffered from breast cancer and 26 (18.1%) had other cancers. The treatment contributes to oocyte retrieval in 133 cases, oocytes freeze in 55 cases and embryos freeze in 66 cases. Here we report the results by cancer type.

### Gynecological Cancer

There were 166 patients in this group. The mean±SD age was 30.1±6.3 years (range: 15-45 years). The cancer type and pathologies are listed in Table 2. The most referred cases were ovarian cancers with the pathology of the epithelial cell (43.7%).

**Table 2. Different pathologies in gynecological cancers**

| Ovary n=108 | Uterus n=44 | Cervix n=14 |
|---|---|---|
| **Epithelial (62.2%)** | Adenocarcinoma (64.0%) | Adenocarcinoma (28.5%) |
| **Non-epithelial (20.4%)** | Leiomyosarcoma (28.0%) | Squamous cell carcinoma (28.5%) |
| **Unknown (17.3%)** | Choriocarcinoma (4.0%) | Rhabdomyosarcoma (7.1%) |
| | Unknown (4.0%) | Clear cell carcinoma (7.1%) |
| | | Unknown (28.5%) |

In these cases, 47 (28.9%) underwent a total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH+BSO) based on the stage, cancer type, and the patient age. Biological pregnancy could occur with surrogacy in survivors that we did not have in this duration of follow-up.

As mentioned, 79 (47.5%) participants entered into the oocyte retrieval cycles. In the follow-up, 23 cases (13.9%) got pregnant in this group (Table 3), 12 cases were after oocyte retrieval from which 7 patients got pregnant spontaneously and 5 with ART methods. The difference in pregnancy rate within ovarian, uterine, and cervical cancer was not significant (p=0.132). The other 11 pregnancies occurred in the patients who did not experience oocyte retrieval cycles including 7 spontaneous and 4 with ART methods. We also reported the results of each subgroup of gynecological cancers including ovarian, uterine, and cervical.

**Table 3. Demographic, lab data and cycle characteristics in cancer groups**

| Outcome Variable (Mean±SD) | Gynecological Cancers | Breast Cancer | Others | p |
|---|---|---|---|---|
| **Age (Years)** | 30.1±6.3 | 33.6±5.7 | 27.5± 7.0 | <0.000 |
| **Married (%)** | 66.8 | 54.2.5 | 50.0 | 0.025 |
| **Positive Infertility History (%)** | 23.3 | 20.0 | 23.1 | 0.346 |
| **AFC (n)** | 5.2±5.3 | 7.8±5.1 | 5.7±5.7 | 0.169 |
| **FSH (mU/ml)** | 9.5±12.3 | 15.1±17.6 | 15.8±21.9 | 0.420 |
| **AMH (ng/ml)** | 2.3±3.0 | 3.0±4.2 | 2.1±2.2 | 0.484 |
| **Gonadotropin Dose (n)** | 35.6±14.0 | 34.1±13.4. | 34.7±12.6 | 0.837 |
| **Induction Days (n)** | 10.9±2.1 | 9.9±2.1 | 10.4±2.8 | 0.310 |
| **Punctured Eggs (n)** | 6.4±6.2 | 7.0±6.0 | 7.6±5.2 | 0.689 |

AFC: antral follicle count; FSH: follicle-stimulating hormone; AMH: anti-Mullerian hormone; mU/ml: milliunit/milliliter; ng/ml: nanogram/milliliter; n: number

### Ovary

The mean±SD age was 29.2±6.4 years (range: 15-45 years). In this subgroup, 100 (92.8%) cases were a candidate for ovulation induction and a total of 57 (57.0%) participants were entered into the cycles. Of these patients, 86 (80.3%) cases had fertility-sparing surgeries and 22 (19.6%) underwent TAH+BSO. The 8 remained patients were a candidate for other methods such as egg/ovum donation or cryopreservation, but only 1 candidate for ovum donation continued her treatment and could get 10 frozen embryos from her sister's oocytes.

In the follow-up, 13 (12.2%) pregnancies (8 spontaneous and 5 with ART) occurred that 9 (69.2%) were in the patients who entered into the oocyte retrieval cycles and 4 (33.3%) belonged to the patients who conceived spontaneously. The rate of pregnancy was not statistically different (p=0.662) between the induction or non-induction ovulation group.

### Uterine

The mean±SD age was 32.4±5.7 years (range: 17-44 years). In uterine cancer, 39 (88.6%) cases were suitable for oocyte retrieval and 16 (36.3%) women started the cycles. Of these patients, 8 (50.0%) had fertility-sparing surgeries and the other half underwent TAH+BSO. Two participants were a candidate for ovarian tissue cryopreservation and none of them were successful due to difficult access to their ovaries.

Totally 10 (22.7%) cases could be pregnant that 4 (40.0%) occurred in the patients who entered the oocyte retrieval cycles and the other 6 (60.0%) in the

non-induction group were not statistically meaningful (p=0.409).

**Cervix**

The mean±SD age was 29.2±6.3 years old (range: 18-41 years). Thirteen (92.8%) patients were a candidate for oocyte retrieval and 6 (42.8%) cases entered into the cycles. In the oocyte retrieval group, 8 (61.5%) cases underwent TAH+BSO. Unfortunately, none of the patients in this subgroup were successful to be pregnant.

**Breast**

The mean±SD age was 33.6±5.7 years (range: 19-45 years). In this group, 24 patients (22.4%) had been referred to our clinic after their chemotherapy or radiotherapy whereas, 3 patients were not a good candidate for fertility preservation due to old age, low ovarian reservoir, or positive history of infertility. Eighty-three patients (77.6%) had been referred before the beginning of their chemo-radiation therapy. Among this subcategory, just 39 (36.4%) patients decided to begin oocyte retrieval and 68 (63.5%) patients were not willing to do it. Indeed, we excluded 3 patients due to lacking the necessary criteria.

However, 6 (5.7%) pregnancies happened after completing cancer treatment (3 pregnancies in the oocyte retrieval group and 3 in the cases not entered into the cycles) that 2 of them happened spontaneously and 4 others occurred with the help of ART methods. We did not record pregnancy in the category of the patients who did refer before cancer treatment for the reason that they were still under treatment or follow-up and the time interval was not enough to judge the pregnancy outcome in this group. The follow-up results in all cancer types are abstracted in Table 3.

**Others**

The mean±SD age was 27.5±7.0 years (range: 12-42 years). This group had the youngest patients among the 3 groups (p<0.000). The distribution of different cancers is shown in Figure 1.

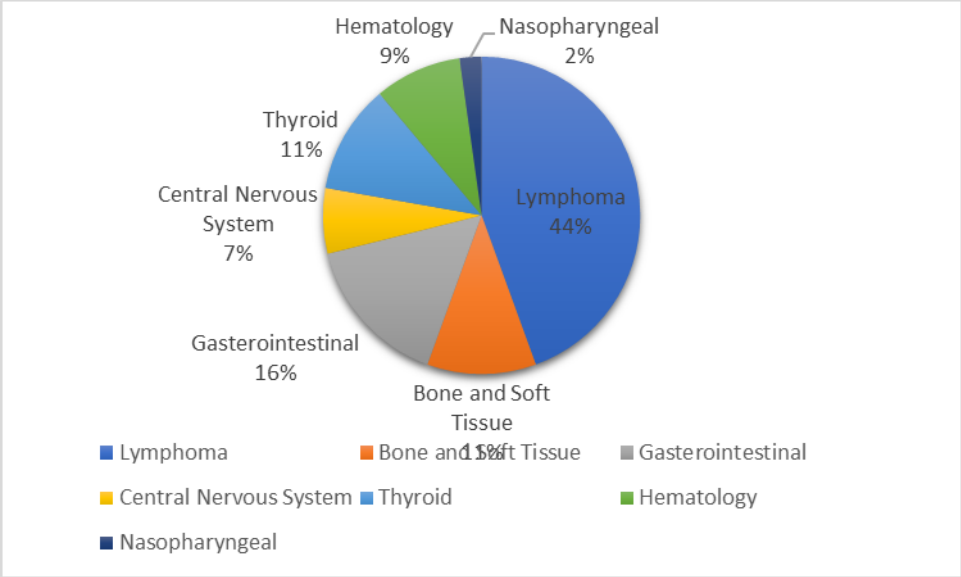


**Figure 1.** **Cancer subcategories and their proportion**

In this group, 26 patients (40.6%) were referred after their chemotherapy, radiotherapy, or radioactive Iodine courses (in thyroid cancers) and 38 (59.3%) cases before treatment. Totally, 95.6% were candidates for oocyte retrieval. Thirty-two (50.0%) patients decided to enter into oocyte retrieval cycles.

In the follow-up, 4 (6.2%) pregnancies happened. Two of them occurred after cancer treatment and 2 before treatment. Two pregnancies occurred spontaneously and 2 by ART due to positive infertility history.

***Comparing between groups***

The difference in age and marital status were statistically different between the 3 groups of cancer. Otherwise, AFC, FSH, and AMH, which were determined as ovarian reserve indicators, were not statistically different. The demographic, lab data and cycle characteristics in cancer groups are listed in Table 3.

In reviewing the gonadotropin dose used, the duration of inductions (from the first gonadotropin injection to the last one), and the punctured eggs for each patient, there was no statistically significant between groups (the p values are illustrated in Table 3).

Comparing these 3 groups, in gynecological cancers, we had a higher rate of pregnancies (11.7% compared with 5.7% in breast cancer and 6.6% in others); however, this difference was not statistically significant (p=0.700).

In the follow-up of 252 patients so far (this study is ongoing and new cases are recruiting and the others are following), we tracked the clinical and pregnancy outcome, in both categories including before and after treatment and the results are listed in Table 4.

**Table 4. Oncofertility patients' follow up based on cancer type before and after treatment based on cancer type**

| Follow Up | Gynecological Cancers (%) n= 137 | | Breast Cancer (%) n= 70 | | | | Others (%) n= 45 | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| **Treatment** | | | **Before** | | **After** | | **Before** | | **After** | |
| **Oocyte retrieval** | - | + | - | + | - | + | - | + | - | + |
| **Expired** | 2.2 | 1.5 | 4.3 | 1.4 | 0 | 0 | 2.2 | 4.4 | 2.2 | 6.7 |
| **Under Cancer Treatment** | 5.8 | 5.1 | 8.6 | 2.9 | 2.9 | 1.4 | 8.9 | 2.2 | 4.4 | 4.4 |
| **Cancer Treatment Completed** | 32.1 | 37.2 | 31.4 | 14.3 | 14.3 | 5.7 | 17.8 | 11.1 | 11.1 | 13.3 |
| **No Access to the Patients** | 8.8 | 7.3 | 5.7 | 4.3 | 1.4 | 1.4 | 4.4 | 2.2 | 0 | 4.4 |
| **Pregnancy** | 6.6 | 7.3 | 0 | 0 | 2.9 | 2.9 | 0 | 2.2 | 0 | 4.4 |
| ***Spontaneously*** | 4.4 | 4.4 | 0 | 0 | 1.4 | 0 | 0 | 2.2 | 0 | 2.2 |
| ***By ART[a]*** | 0.7 | 1.5 | 0 | 0 | 0 | 2.9 | 0 | 0 | 0 | 2.2 |

a: ART: assisted reproductive techniques

## Discussion

Nowadays, an increasing number of cancer survivors, progress in cancer treatment methods along with the improvement of infertility treatment results in the use of fertility preservation methods (8). Oncofertility is a new multidisciplinary field that gathers the gyneco-oncologists, infertility specialists, general oncologists, biologists, psychologists, endocrinologists and general practitioners all together for cooperation (18).

Some researchers believe that a certain team should be responsible for a consultation about oncofertility. Bastings et al. discussed fertility preservation after getting advice from an oncologist and many patients declared that it was difficult to make decisions whether to consider ovarian tissue damage or begin the cancer treatment as early as possible. The majority of patients said the young age, recent onset of sex, and lack of enough time for making a proper choice, have made the decision-making process difficult (5).

The nurses may have the best position to do patient education and this requires explaining pregnancy risks and fertility preservation methods as well as strategies to facilitate the necessary fertility processes (19). In the current study, this task was done by an infertility fellowship and experienced obstetrical midwifery, an expert in fertility, and oncofertility to explain the different fertility preservation methods, advantages and disadvantages of each, the cost, and the minimum time needed for beginning the process.

The patients would be satisfied by oncofertility consultation but may believe it needs improvement. The problems are a limited time for consultation, lack of asking questions, not being supported by the counselor and the benefits and disadvantages of any choice were not well clarified (5).

In our study, other problems such as hymen damage, referring to other infertility centers for fertility preservation, high cost of treatment, being high risk to get hormonal treatment in the hormone-dependent cancers, and the possibility of poor response to treatment were some barriers that prevent the patients from choosing a suitable fertility preservation method.

Hymen damage is a native socio-geographical issue that needs to be resolved by using serious legal approaches. In the telephone interview with the patients, they were asked about the reasons for choosing other infertility centers and our clinic being over-crowded and congested as a tertiary referral center was the main reason.

Formerly, it had been thought that a decrease in fertility ability in cancer patients is due to cancer treatment; though research has shown that even before cancer therapy, malignancy harms fertility (20) because of catabolism and malnutrition state (21). Also, it was revealed that ovarian response to controlled ovarian stimulation is lower in cancer patients considering the number of oocytes retrieved (22), and also it was mentioned poorer response in hormone-dependent cancer compared with non-hormone dependent cancers (23). However, a meta-analysis claimed that there is no difference in ovarian

response to stimulation between cancer and non-cancer patients (24).

Most of the studies determine the successful response as the number of eggs retrieved and there are limited studies about the quality of embryos or the rate of pregnancies, but these limited studies also showed comparable pregnancy rates between breast cancer patients and other elective IVF patients (25). In the current study, we also gathered the data of eggs retrieved and compared between various cancers and concluded that there was no statistical difference between them.

We also collected the patients' pregnancy data after the fertility preservation process, but because of the short follow-up interval, and that some patients had not yet completed the treatment process and were not allowed to be pregnant, the judge may not entirely be correct. For example, having a low pregnancy rate in breast cancer might be due to the time break of 5-year needed to postpone pregnancy to be sure of no cancer recurrence.

Previous studies showed a unique association between BRCA-1 gene mutation and infertility and decreased AMH levels in breast/ovarian cancer risk (26, 27). This happened because of the impairment of repairing DNA double-stranded breaks due to mutant BRCA-1 (28). Yet, Johnson et al. showed that AMH level is decreased in patients with BRCA-2 mutation and patients with BRCA-1 mutation have similar AMH level compared to the control group (29). Regardless of gene mutation, it was declared that there is a significant positive association between high circulating AMH levels and breast cancer risk especially in $ER^+/PR^+$ cancers (30). In this study, we observed no statistically significant difference between AMH levels in cancer groups which might be due to the small sample size.

Indeed, cryopreservation of embryos or oocytes needs ovarian hyperstimulation, and the risk of increased estrogen levels should be discussed. But it seems tamoxifen or letrozole in conjunction with gonadotropin may be safer for women with ER + tumor (31, 32). Nevertheless, there is no statistically significant difference in ovarian stimulation outcomes whether letrozole is used in breast cancer patients (33).

The best fertilization result is achieved in letrozole cycles when hCG is given at 19.5-20.5 mm follicle size compared with the customary 17-18 mm and since the stimulation length is no longer in letrozole + gonadotropin cycle, this difference is more likely because of earlier formation of antral space in using letrozole (34). The reason may be due to decreased oocyte quality in the letrozole cycle at the same size as oocyte compared with the non-letrozole cycle (33).

In our study for the patients suffering from breast cancer with positive hormone receptors, letrozole was used for ovulation induction. We used the GnRH-antagonist protocol in both cancer groups by random start and conventional start since our document supported that the random start is as effective as a conventional start (35).

Opposing the thought of lower induction of ovulation response in breast cancer patients, confirmed that they have neither compromised fertility reserve nor reduced ovarian response to ovulation induction (24, 33). This is partly due to the small sample size of previous studies, heterogenicity in inclusion criteria, and having milder stimulation protocol for breast cancer patients in past studies (33). Similarly, we concluded there is no statistically significant difference in ovarian reserve and ovarian response to induction cycles between breast cancer and other cancers.

It is mentioned that ovarian induction drugs taken with standard protocol doses, do not increase the breast cancer risk and it was just said that long use of clomiphene other than the limited present indications (for example to cure infertility due to anovulation in group WHO II as the first line) must be limited because of a possible increase in breast cancer risk (17). Also, pregnancy in patients who had breast cancer previously, not only does not increase the risk for cancer recurrence, maternal side effects, or congenital malformations but also is associated with a reduced risk of death in these patients (36).

For women seeking reproductive independence or without a sexual partner, ovum freeze is a standard fertility preservation method (37). In our research, fertility preservation methods had been done using ovum and embryo freeze and as it was mentioned, ovum freeze was performed in the cases in which the patient was single or was chosen after complete consultation according to personal reasons. Embryo freeze in the other cases was preferred.

In ethical considerations, different theories have been proposed (38). Pennings et al. claim everyone has the right to reproduce although it may be challenging when the right to reproduce is outweighed by others' rights. On the other hand, the child may have a higher possibility to losing the parent in addition to the possibility of inheriting the disease (39). Marinating morale in these patients is very important and conceiving may be a strong motivation for them to be alive (40). A possible lag in the treatment may be happened due to fertility preservation, although this interval time did not change the cancer treatment, mortality, and recurrence rate among women who underwent fertility preservation or not (41).

We have performed this research in an academic tertiary center for an 8 years follow-up; so that the most complicated disease and diversity could be seen among our patients. Besides, this center could be one of the pioneers of fertility preservation in the region.

We recruited all cancer patients, despite the previous studies which used the non-cancer patients doing elective IVF for infertility as control. The infertility rate in the elective IVF group could be a confounding factor in these studies. Also, we used a random start

antagonist protocol which leads to time-saving in both groups so that we could begin the induction cycle on the first day of patient referral. This process is much more important in cancer patients. As our results show the mean induction days last for 9-10 days which is even lower than 2 weeks. Furthermore, we used AFC as an ovarian reserve indicator, since it is not an invasive procedure, can be done on all days of the ovarian cycle, and is not influenced by hormonal changes.

However, we know that an 8-year follow-up may not be enough and the patients need to be followed for a longer time. Designing a follow-up system in the oncofertility field is very valuable since the patients leave the infertility clinic to treat their cancer and may not come back by themselves until their oncologists refer them again which may last some years later. Our follow-up using phone calls had a response rate of about 86.1% which was much more than the other studies (34.5%) **(42)**.

The limitation of our study was the brief and short information in the patients' documents because of a hurry in beginning the fertility preservation method and cancer treatment. This problem was much in the patient who did not come back which made the current and future studies, more difficult. Also, the small sample size of the group recruited in oocyte retrieval processes may limit the judgment about the comparative results.

We are at the beginning of this path and we wish to follow more patients via a national registry system and for a longer duration. We are proceeding with the study, and tracking the lab, clinical results, and pregnancy complications and outcomes such as a live birth. It is also recommended the cryopreservation in male cancers.

## Conclusion

Many patients and even their therapists are unfamiliar with the methods of fertility preservation, and when they consider it, the golden time is usually passed. Therefore, having a good consultation with the survivors and patient education may be the most important issue that led to a timely referral for preserving fertility in cancer patients. Our results indicate that an effective multidisciplinary oncofertility team is mandatory for prompt referral of the cancer survivors to preserve fertility. Despite the previous claim that breast cancer survivors have a lower chance for fertility and good ovarian reserve, such a difference was not observed in our study.

## Acknowledgments

This manuscript was originated from a thesis by MS for fulfillment of clinical specialty in obstetrics and gynecology at Tehran University of Medical Sciences, Tehran, Iran. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

## Ethical Consideration

This study was approved by Ethics Committee of Tehran University of Medical Sciences (Reference number: IR.TUMS.IKHC.REC.1397.193). All participants read and signed the informed consent before the study initiation. This study was performed due to the Helsinki declaration.

## Funding source

None.

## Authors' contributions

B.HR: Project development, M.G: Manuscript writing, E.STN: Project development, M.M: Data collection and management, M.S: Data management, Manuscript writing.

## Data availability

The data of this study would be available upon request. Further inquiries can be directed to the corresponding author.

## Conflict of Interest

The authors declare no conflict of interest.

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**How to Cite This Article:**

Hossein Rashidi, B., Ghaemi, M., Shahrokh Tehrani, E., Mohebbi, M., Savari, M. Preserving Fertility and Its Outcomes in Iranian Women with Cancer: A Longitudinal Cohort Study. J Obstet Gynecol Cancer Res. 2023; 8(5):446-56.