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Fertility Preservation in Young Women With Breast Cancer: A Review

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ABSTRACT

Fertility preservation is a major concern in young patients diagnosed with breast cancer and planning to receive multimodality treatment, including gonadotoxic chemotherapy with or without age-related decline through long-term endocrine therapy. Most breast cancer patients undergo multimodality treatments; many short-term and long-term side effects arise during these therapies. One of the most detrimental side effects is reduced fertility due to gonadotoxic treatments with resultant psychosocial stress. Cryopreservation of oocytes, embryos, and ovarian tissue are currently available fertility preservation methods for these patients. As an adjunct to these methods, *in vitro* maturation or gonadotropin-releasing hormone agonist could also be considered. It is also essential to communicate well with patients in the decision-making process on fertility preservation. It is essential to refer patients diagnosed with breast cancer on time to fertility specialists for individualized treatment, which may lead to desirable outcomes. To do so, a multimodal team-based approach and in-depth discussion on the treatment of breast cancer and fertility preservation is crucial. This review aims to summarize infertility risk related to currently available breast cancer treatment, options for fertility preservation and its details, barriers to oncofertility counseling, and psychosocial issues.

Keywords: Breast Neoplasms; Cancer Survivors; Fertility Preservation; Pregnancy

INTRODUCTION

The incidence rate of breast cancer is the highest among female cancer patients in Korea, with a five-year survival rate greater than 90% [1]. The development of anticancer agents has led to improved treatment outcomes, which in turn increased the life expectancy of cancer survivors. Thus, the quality of life of cancer survivors after oncologic therapy has gained prominence in the management of breast cancer patients. Breast cancer is becoming more common in women of reproductive age. Fertility-preserving medicines and quality of life following cancer

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Conflict of Interest

The authors declare that they have no competing interests.

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therapy are of particular concern to these individuals. Patients who received fertility-preserving therapies prior to cancer treatment reported that these treatments had a beneficial impact on their quality of life following cancer therapy [2]. In addition, a survey on cancer survivors' attitudes and experiences revealed that 76% of young female cancer patients without children desire to conceive, and 35% of those with children desire to have another child in the future [3].

Gonadotoxic therapy during cancer treatment, depending on the type, dose, and frequency of anticancer agents, may cause a decrease in reproductive function and premature ovarian insufficiency. It is essential to inform cancer patients of reproductive age about the side effects of gonadotoxic medicines and the available fertility options before treatment, to achieve optimal fertility preservation and enhance the quality of life. In addition, it has been reported that the fear of impaired reproductive function in young breast cancer patients may affect their choice to initiate or continue tamoxifen treatment [4]. Thus, accurate information and treatment chances regarding fertility preservation options should be provided to patients.

Fertility preservation in cancer patients is becoming part of mandatory treatment, rather than a matter of choice, in the whole treatment process. The American Society of Clinical Oncology (ASCO) also recommends a timely referral of patients to a fertility clinic before the initiation of cancer treatment [5]. As the number of young breast cancer patients rises year after year, it is essential for healthcare professionals caring for breast cancer patients to be well acquainted with the topic. In this review, the effect of anticancer therapy on reproductive function and mental health and various available strategies for fertility preservation are discussed to provide the best available fertility preservation tailored for each patient.

IMPACT OF SYSTEMIC TREATMENTS FOR BREAST CANCER ON FERTILITY

The treatment strategy of breast cancer is determined by considering various factors, including the subtypes, stage, and germline *BRCA* status of breast cancer, as well as the age and menopausal status of breast cancer patients. Systemic treatment involves various combinations of cytotoxic chemotherapy, hormone therapy, targeted therapy, and immunotherapy [6]. Therefore, various factors affect the risk of treatment-related amenorrhea (TRA) and subsequent post-treatment ovarian insufficiency (POI) in breast cancer patients. In this section, we discuss the data on the impact of these agents on fertility and the potential mechanisms underlying the impact.

Cytotoxic chemotherapy

Cytotoxic chemotherapy has been one of the most important treatment strategies for breast cancer, and it generally affects actively dividing cells which include gonadal cells. Research on the gonadal toxicity of systemic treatments has largely focused on these chemotherapeutic agents. The most important drugs that are commonly used for breast cancer and affect fertility include cyclophosphamide, doxorubicin, and taxanes. These drugs generally cause TRA in up to 83.6% of patients [7], and around 43.6% of patients had TRA at one year and 18.9% at two years after treatment initiation in another study [8]. In patients with TRA, around 70% recovered their menstrual function in one year and 90% in two years [9]. Even if women recover from TRA and begin their menstruation; however, ovarian reserve and patients' fertility may decline after cytotoxic chemotherapy. Several factors are associated

with TRA and recovery from TRA. Patient factors include age, pre-treatment ovarian reserve, and germline *BRCA* pathogenic variants [10]. Treatment-related factors include types of chemotherapy and their doses and duration [10].

Age, which correlates with pre-treatment ovarian reserve, is the most crucial patient factor associated with gonadal toxicity [10]. Patients aged older than 35 are three times more likely to experience TRA compared to those younger than age 30 [8]. Also, the same chemotherapy regimen exhibit different risks of TRA by age group; those aged ≥ 40 being at high risk, 30–39 at intermediate risk; and < 30 at low risk [11].

Patients with germline *BRCA1/2* mutation constitute a unique population regarding fertility. Pathogenic mutation in germline *BRCA* results in impaired homologous recombination DNA repair [7]. Defects in the DNA repair mechanism result in the accumulation of DNA damage and susceptibility to DNA damage over time [12]. It is controversial whether *BRCA* carriers have decreased ovarian reserve and elevated susceptibility to chemotherapy [13]. *BRCA* carriers tend to experience menopause 1–3 years earlier [14], and their cryopreserved ovarian tissue shows a lower number of oocytes per fragment compared to that of non-carriers (0.08 vs. 0.14, $p = 0.193$) [15]. On the other hand, in clinical studies, there were no differences in rates of TRA and anti-Müllerian hormone (AMH) levels between *BRCA* carriers and non-carriers with breast cancer who received chemotherapy [16,17]. Further studies are needed to determine the exact risk of TRA and POI in *BRCA* carriers receiving chemotherapy.

Among the cytotoxic chemotherapy agents, cyclophosphamide, an alkylating agent, poses the greatest risk of TRA and POI development. Patients treated with the agent have more than double the chances of developing TRA compared to patients who were not (odds ratio [OR], 2.25, $p = 0.006$ [18]. The effect of cyclophosphamide is associated with possible damage to the non-growing primordial follicle pool, which makes up the ovarian reserve [10]. This is implicated in the observation that AMH levels remain lower after treatment in patients who receive alkylating agents compared to those who did not [19].

Doxorubicin, an anthracycline, and taxanes such as docetaxel and paclitaxel also cause gonadal dysfunction. However, the risks are lower than those of cyclophosphamide (OR, 1.26, $p = 0.0003$ for anthracyclines; OR, 1.39, $p = 0.0008$ for taxanes) [18]. Similar to cyclophosphamide, these agents affect the ovarian reserve; according to a study, patients who received those agents show a decrease in AMH levels which remain very low, although the levels slightly but significantly recover after three years [17]. In clinical practice, these agents are often administered in combination or in sequential order. The risk of TRA seems similar between different schedules, as a similar rate of TRA was reported between a combination regimen and a sequential regimen (81% vs. 80%) [10,20] and between a dose-dense schedule and a standard regimen (OR, 1.00, $p = 0.989$) [10,21].

Hormone therapy

Premenopausal patients with hormone receptor-positive breast cancers often receive hormone suppression with tamoxifen for 5 to 10 years [6]. There was a significant increased risk of TRA with tamoxifen treatment (OR, 1.48, $p<0.00001$) [18], but the effect of tamoxifen seems largely reversible. In a study on the patients who recovered from TRA after chemotherapy and received tamoxifen with or without goserelin over five years (ASTRRA study), menstruation was restored in 69% of overall patients and 91% of patients aged < 35 [22]. Serum follicle-stimulating hormone (FSH) levels and estradiol (E2) levels were also restored in majority of

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these patients (98% and 74%, respectively) [22]. Also, recovery of AMH levels did not differ between patients who received endocrine therapy and those who did not [17].

Anti-human epidermal growth factor receptor 2 (HER2) therapy

Treatment of HER2 positive breast cancer involves anti-HER2 agents including trastuzumab, pertuzumab, lapatinib, ado-trastuzumab emtansine (T-DM1), and trastuzumab deruxtecan [6]. Analysis of data from a study comparing T-DM1 with trastuzumab plus paclitaxel (ATTEMPT trial) showed significantly lower 18-month rate of TRA in patients who received T-DM1 (24% vs. 50%, $p = 0.045$), suggesting safer gonadal toxicity profiles in anti-HER2 monotherapy compared to cytotoxic chemotherapy combination [23]. Also, in the additional analysis in the ALTTO trial, dual inhibition of anti-HER2 therapy by combination or sequential treatment did not result in an increased incidence of TRA compared to anti-HER2 monotherapy [24]. One study showed superior recovery of AMH levels in patients who were treated with chemotherapy and trastuzumab compared with those who were treated with chemotherapy only (57.1% vs. 36.8%, $p < 0.05$) [25]. In the preclinical part of the study, the blood vessels of the ovary showed high expression of HER2, and it was hypothesized that the inhibition of HER2 may have protected from the potential gonadal toxicity mechanism of cytotoxic chemotherapy [25]. Collectively, the risk of TRA with anti-HER2 agents is relatively low.

Other targeted therapy

Cyclin dependent kinase 4/6 inhibitors are being researched in early breast cancer settings, but there is little data on the gonadal toxicity profiles. An exploratory analysis from the PENELOPE-B trial, a phase III trial on endocrine therapy with or without palbociclib in hormone receptor positive breast cancer, the levels of E2, FSH, and AMH were all similar between groups, and a similar proportion of patients had the premenopausal hormone levels at the end of treatment (48.7% in palbociclib arm and 47.7% in control arm, $p = 0.863$) [26].

Poly ADP-ribose polymerase (PARP) inhibitors are also used in the early and advanced breast cancer settings. Currently, there is no published data on the effect of PARP inhibitors on fertility in humans. In an experiment on *BRCA* wild-type mice, a combination of chemotherapy and olaparib significantly decreased primordial follicles by 36% compared to that without olaparib ($p < 0.05$) [27]. The result suggests potential gonadal toxicity of PARP inhibitors, and further preclinical and clinical studies are warranted.

Immunotherapy

Currently, immune checkpoint inhibitors in the neoadjuvant and metastatic setting are being used in clinical practice for breast cancer [6,28]. While data on the direct effect of immune checkpoint inhibitors on POI is scarce, immune checkpoint inhibitors may cause thyroiditis, adrenalitis, and hypophysitis [29], all of which may affect fertilization through impaired hypothalamic-pituitary-ovarian axis hormonal regulation. Appropriate hormone replacement would be necessary to maintain fertility in these cases, which require multidisciplinary management with specialists in endocrinology and reproductive medicine.

FERTILITY PRESERVATION STRATEGIES FOR YOUNG WOMEN WITH BREAST CANCER

To select the optimal method of fertility preservation, it is necessary to consider several factors, including the age of the patient, the severity of the disease, the cancer stage, the

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urgency of immediate treatment, marital status, future pregnancy desire, and the maximum available interval between controlled ovarian stimulation (COS) and the initiation of cancer therapy. Currently, there are several options for fertility preservation. The decisions on whether to cryopreserve oocyte, embryo, or ovarian tissue and whether to use gonadotropin-releasing hormone agonist (GnRHa) in addition to systemic therapy should be made after careful consideration of each patient's situation, medical status, needs, and goals.

Oocyte and embryo cryopreservation

Embryo cryopreservation is typically performed on patients with a male partner; it is a technically stable method and provides a high chance of fertility for the patient. Oocyte cryopreservation is performed on patients without a male partner. With recent advances in cryopreservation technology, the outcomes of oocyte freezing are comparable to embryo cryopreservation. Both methods are clinically well-established and widely implemented in practice. During oocyte and embryo cryopreservation, COS is performed to maximize the number of cryopreserved oocytes or embryos for higher chances of conception. Usually, it takes 10 to 12 days to complete ovarian stimulation and oocyte retrieval. These procedures should be done before systemic anti-cancer therapy starts. To adequately inform the patients about available choices and minimize the delay in cancer therapy, it is crucial to refer them to a fertility preservation clinic as soon as possible. The optimal ovarian stimulation method is selected to obtain the maximum number of oocytes in a limited period. The optimal number of oocytes for cryopreservation has been the subject of discussion. The ovarian response to stimulation varies based on the patient's age and ovarian reserve; however, the goal is to obtain 10 to 15 oocytes [30]. Most patients have only one to two chances of ovarian stimulation before cancer therapy; thus, choosing the best protocol for stimulation is critical. The most commonly used protocol is the GnRH antagonist protocol; it has a relatively short stimulation duration and a decreased risk of ovarian hyperstimulation syndrome (OHSS). The ovarian function of patients is initially evaluated with AMH levels, FSH levels, and antral follicle count (AFC). Based on these tests, the starting dose of gonadotropin for COS is determined. After administering gonadotropin, a GnRH antagonist is given appropriately to inhibit premature ovulation. Conventionally, when two to three follicles reach 17 to 18 mm in diameter, triggering medication such as human chorionic gonadotropin (hCG) and/or GnRHa for final maturation is given. In breast cancer patients, triggering criteria are usually modified as the largest follicle diameter reaches to 20 mm. Transvaginal ultrasound-guided oocyte retrieval is performed 34 to 36 hours after triggering. For both oocyte and embryo cryopreservation, the oocyte retrieval procedure is identical. For embryo cryopreservation, fertilization occurs in addition to the oocyte retrieval procedure. There has been much effort in attaining the maximal yield of oocytes in breast cancer patients undergoing fertility preservation by utilizing various clinical markers, including BRCA1/2 mutation status, hormone receptor status, and blood markers [31,32]. When a BRCA1/2 mutation is identified, the lifetime risk of developing ovarian cancer ranges from 10% to 50%. In these individuals, cryopreservation of oocytes or embryos is favored over ovarian tissue freezing. Preimplantation genetic testing may be considered for detecting BRCA1/2 mutational status in fertilized embryos [33].

There have been concerns about delayed chemotherapy due to the time required for oocyte cryopreservation. However, current evidence suggests that fertility-preserving procedures do not delay the time interval between surgery and chemotherapy [34]. Furthermore, random-start ovarian stimulation did not delay the initiation of neoadjuvant chemotherapy [35].

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COS and oocyte retrieval are reasonably safe and convenient outpatient procedures that may be performed at a daycare unit. The complication risk is minimal but possible; among the probable consequences are intraperitoneal hemorrhage due to needle puncture and ascites from OHSS. In those with a high risk of developing OHSS, cabergoline or GnRH antagonists could be given for prevention. Even though OHSS occurs, cancer patients are at minimal risk for further progression since embryo transfer is not carried out directly afterward; symptoms usually regress spontaneously in a short time.

Pregnancy outcomes following the completion of cancer therapy are currently limited as cases are beginning to accumulate. When the pregnancy results of frozen embryo transfer in cancer survivors are compared to those of patients with tubal factor infertility, the cumulative pregnancy rate per transfer and cumulative live birth rate per transfer was similar between the two groups (37% vs. 43%, $p = 0.49$, and 30% vs. 32%, $p = 0.85$, respectively) [36]. Cobo et al. [37] reported pregnancy outcomes after oocyte cryopreservation of cancer patients (n = 80); in a fresh embryo transfer cycle, the clinical pregnancy rate per transfer was 41.4%, and the live birth rate was 31%. When the cryo-transfer of the surplus embryo cycle was included, the cumulative live birth rate per patient was 35.2%. The pregnancy outcomes of cancer survivors are not different from those of women who underwent elective fertility preservation. Further analysis of pregnancy outcomes from cancer survivors who return to use their cryopreserved oocytes or embryo and long-term follow-up analysis is necessary.

COS methods implemented in breast cancer patients

Random-start ovarian stimulation

In a conventional COS procedure, ovarian stimulation commences in the early follicular phase, just after the start of the menstrual cycle. However, as prompt initiation of cancer therapy is crucial, waiting for the onset of menstruation among cancer patients is unrealistic. The advent of the multiple waves theory, which states that recruitment of a group of follicles is done multiple times throughout a single menstrual cycle, enabled the initiation of ovarian stimulation at any time during the menstrual cycle [38]. This process is coined the random-start and luteal-phase ovarian stimulation regimen, which is distinguished from conventional stimulation. The development of the random-start method is a milestone in fertility preservation technology that enables fertility preservation in cancer patients without delay in cancer therapy. The pitfall of the random-start method, which is the difficulty of utero-ovarian synchronization and preparation for embryo transfer, is not a concern for cancer patients, as cryopreservation *per se* is the primary goal. Compared with conventional methods, the total dose of gonadotropin tends to be slightly higher, and the stimulation day of the cycle tends to be slightly longer in the random-start method. However, no difference in the total number of retrieved oocytes and mature oocytes was noted between the two methods [39,40]. Random-start ovarian stimulation, which shortens the interval between the start of COS and oocyte retrieval, works as a practical and feasible method for patients who have to undergo chemotherapy immediately.

Combination of an aromatase inhibitor for ovarian stimulation

Unlike other types of cancers, the hormone-dependent nature of breast cancer raises particular concern that supra-physiologic E2 levels caused by ovarian stimulation may negatively impact cancer progression and future prognosis. However, the combination of aromatase inhibitor (letrozole) during COS eliminates such a concern as it inhibits the rise of serum E2 levels. During COS, letrozole is administered 5 mg orally with the start of gonadotropin. It is given daily until the triggering day; after oocyte retrieval, letrozole is

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continued for about a week until serum E2 levels fall below 50 pg/mL. With the letrozole combination method, exposure to high serum E2 levels decreases compared to the standard COS method, although the number of oocytes acquired remains similar. Also, compared to those who had not undergone any fertility preservation procedures, the recurrence risk of breast cancer and disease-free survival rates stayed similar, and this also held for patients with BRCA mutation [39,41-44].

Dual triggering

As the last step of the COS before oocyte retrieval, triggering is done for the final maturation of oocytes. As the triggering agents, either hCG, GnRHa, both of them at the same time (dual trigger), or both at the same time interval (double trigger), could be used. In one study comparing different triggering agents in breast cancer patients, the GnRHa trigger group showed a greater oocyte maturation rate, fertilization rate, and the number of cryopreserved embryos compared with the hCG trigger group, with a lower incidence of OHSS as well [45]. This may be attributed to the fact that GnRHa stimulates endogenous FSH and luteinizing hormone (LH) production, creating a more favorable physiological milieu for follicular growth than hCG alone as a triggering agent. However, the incidence of failure or suboptimal response rate after GnRHa triggering has been reported to be as high as 5.2%; risk factors for such failure may include low BMI or low endogenous serum LH [46,47]. In cancer patients, where the chances for fertility preservation are limited to very few, failure during the fertility preservation procedure may have detrimental consequences. Especially in breast cancer patients who routinely incorporate letrozole into COS procedure, there have been reports of a lower yield of mature oocytes or a decreased maturation rate compared to outcomes from the conventional COS cycle. To overcome such potential disadvantages, there were attempts to increase the maturation rate by the delayed triggering of follicles when they reach 20 mm, rather than the conventional 17–18 mm [48]. However, as the GnRHa trigger has a short half-life, possibility of failing to achieve the adequate triggering with suboptimal intrinsic LH surge exist [48]. Using both hCG and GnRHa for triggering could be considered in these patients. A recent retrospective study by Hong et al. [49] revealed that in patients diagnosed with breast and endometrial cancers undergoing COS for fertility preservation with the letrozole protocol, the dual trigger group had an increased number of mature oocytes compared to the recombinant hCG trigger group (6.9 ± 6.0 vs. 4.6 ± 3.6, $p = 0.034$). The rate of OHSS did not differ between the two groups. Thus, in breast cancer patients undergoing the letrozole protocol with a risk of poor maturation rate in retrieved oocytes or with a low expected oocyte yield due to diminished ovarian reserve, dual triggering could be considered an effective method of facilitating oocyte maturation.

Double stimulation

This method involves obtaining a high number of oocytes in a limited time by performing two cycles of COS within one menstrual cycle, each at the follicular and luteal phases. Originally introduced by Kuang et al. [50] in patients undergoing *in vitro* fertilization (IVF) and intracytoplasmic sperm injection, this method involves two oocyte retrieval processes. The initial oocyte retrieval is done following the first round of COS. The second round of COS begins immediately on the following day of oocyte retrieval, followed by the second oocyte retrieval. In other trials examining the efficacy of this approach, variations of the double stimulation regimen utilizing different types and doses of gonadotropin have been shown to be effective. The number of total oocytes, mature oocytes, and blastocysts in the first and second cycles was similar. More importantly, the number of total oocytes, mature oocytes, and embryos from the double stimulation method was greater than that from the

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conventional cycle with a single stimulation [50-52]. Double stimulation could be a feasible method that maximizes oocyte yield. Suppose a sufficient number of oocytes have not been obtained and the time that remains before chemotherapy is not enough for another stimulation after menstruation, then, double stimulation could be an alternative.

Ovarian tissue cryopreservation (OTC)

OTC is a method of preserving ovarian tissue with cryopreservation technique without the ovarian stimulation process. This method is suitable for prepubertal girls or pre-menarchal adolescents diagnosed with malignancy and patients unable to undergo COS because of an urgent need for cancer therapy. Although clinical experiences worldwide are still limited, this is not considered an experimental method anymore, and it is being recognized as one of the clinically established methods for fertility preservation [53]. It has been proven technically feasible, as over 200 live births have been reported [54]. OTC is considered an ideal fertility preservation method because it can preserve fertility and hormonal production. Another advantage is that there is no delay in chemotherapy as the COS procedure is unnecessary. The downside of this procedure is that laparoscopic operations are necessary for ovarian tissue harvest for cryopreservation and transplantation. After treating the retrieved ovarian tissue with cryoprotectant, it is stored in liquid nitrogen using either a slow-freezing or vitrification technique. When the transplantation is decided, ovarian tissue is thawed and placed either back into a site within the pelvic cavity (orthotopic transplantation) or in another site (heterotopic transplantation) such as the abdominal wall or forearm. It has been reported that the pregnancy success rate following transplantation of cryopreserved ovarian tissue is 26%, which includes both women who conceived naturally and those who conceived through IVF procedure [55]. It is essential to avoid cryoinjury during the freeze-thaw process and minimize ischemic injury during the transplantation procedure to enhance the viability of transplanted ovarian tissues and maximize pregnancy rates following transplantation [56].

Except for patients with metastatic cancers or patients with a very high risk of relapse, OTC in breast cancer patients is generally not a contraindication. There is no consensus on indications of OTC, and no specific guidelines have yet been established. However, performing OTC in patients over 45 years of age is discouraged since older patients have a relatively low follicular reserve, poor graft quality, and lower chances of pregnancy. Although the specific age of patients suitable for OTC is hard to specify, age range between 30 and 40 years has been proposed as ideal. As there are individual variations, chronological age cannot serve as an absolute indicator for determining OTC; a personalized approach to evaluating the benefits and hazards of each patient's circumstance is required.

In a review article by Fleury et al. [57], which analyzed 16 patients diagnosed with breast cancer who underwent OTC and ovarian tissue transplantation (OTT), the transplanted ovary began to function after 1 to 5 months. The grafted tissue maintained its function for as long as 15 months. Though variations in techniques for detecting malignant cells in tissues exist, tumor cells were not found in 272 breast cancer patients across seven studies where their ovarian tissues were cryopreserved [57]. However, a negative result from one fragment of cryopreserved tissues may not totally rule out metastasis in the entire ovarian tissue. A further confirmative study evaluating various combination methods for detecting cancer cells in fragments of cryopreserved ovarian tissues for maximizing sensitivity and specificity is warranted. There have been two reported breast cancer recurrences after ovarian tissue grafting, but it is hard to establish a causal relationship between OTT and breast cancer relapse [57]. The risk of cancer cell transmission through grafted ovarian tissue in breast

cancer patients is considered extremely low [58]. However, the incidence of OTT in breast cancer survivors is relatively scarce; nationwide data accumulation and analysis may aid in further validating the safety and feasibility of OTT after OTC. For a safer implementation of this method, further technical validations to rule out cancer cell seeding in grafted tissue are required. In this article, among 16 patients with breast cancer who underwent OTC and OTT, 12 patients achieved pregnancy at least once, and 14 pregnancies occurred, including twin pregnancies (ten natural and four IVF pregnancies). Ultimately, 11 live births were reported [57]. Although limitations exist, it remains undisputed that OTC is a promising fertility preservation method in patients with breast cancer.

In vitro maturation (IVM)

IVM refers to a method of obtaining immature oocytes without COS and maturing them *in vitro*. Based on the multiple follicular wave concept, IVM is possible at any time during the menstrual cycle of cancer patients, including the luteal phase [59]. Successful cryopreservation of an average of seven oocytes and four embryos per patient in 38 breast cancer patients who underwent IVM without COS was reported [60]. Recent technological breakthroughs in IVM protocols and embryo culture technology have resulted in comparable pregnancy rates between IVM and conventional IVF in infertile patients [61]. However, only four cases of live births have been reported through the IVM protocol [62]. The pregnancy rate using IVM protocols in fertility preservation is lower than for established embryo and oocyte cryopreservation methods; thus, it is still considered experimental. In a study that compared outcomes of 19 cycles of IVF with 14 cycles of IVM for fertility preservation purposes, no significant differences between the two methods were noted in terms of clinical pregnancy rate per embryo transfer and live births per embryo transfer (36.8% vs. 14.3%, $p = 0.15$; 31.6% vs. 7.1%, $p = 0.09$, respectively) [62]. However, a small sample size for comparison precludes concluding that both methods are equally effective. For IVM to be implemented and used widely as an established method for fertility preservation, further studies with larger populations and long-term follow-up are required.

Ovarian suppression with GnRH analogue

GnRHa could be administered before and during chemotherapy to protect ovarian function by inhibiting the circulating levels of gonadotropins (FSH and LH). The precise mechanisms of the protective role of GnRHa on ovarian function are not known. Some suggested mechanisms are that GnRHa mimic a low-gonadotropic environment in pre-pubertal girls and act directly on primordial and primary follicles to protect them.

Two representative randomized controlled trials (RCTs) that investigated the protective effect of GnRHa, namely Final Analysis of the Prevention of Early Menopause Study (POEMS)-SWOGS0230 study and Prevention of Menopause Induced by Chemotherapy (PROMISE)-A Study in Early Breast Cancer Patients-Gruppo Italiano Mammella 6 (GIM6) study, both demonstrated that the addition of GnRHa to chemotherapy prevents ovarian insufficiency compared to receiving only chemotherapy and yields a higher pregnancy rate [63-66]. Similar results were reported in a meta-analysis that analyzed subsequent RCTs investigating the protective role of the GnRHa [67]. Based on these results, combining a GnRHa during chemotherapy in pre-menopausal early-stage breast cancers is suggested as a feasible fertility-preserving option, which lowers the probability of premature ovarian failure.

However, the primary outcome of most clinical studies was chemotherapy-related amenorrhea, not fertility-related measures [63-66]. GnRHa therapy cannot be used as a

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substitute for the currently established fertility preserving method because the degree of protection by GnRHa vary depending on each individual, and this cannot be readily predicted. Furthermore, damage to ovarian reserve is irreversible once an insult occurs. The American Society for Reproductive Medicine (ASRM) and European Society of Human Reproduction and Embryology (ESHRE) also recommend GnRHa treatment as a corollary option along with other fertility preserving methods, or an alternative, if other measures are all contraindicated. Moreover, GnRHa treatment cannot be recommended as an equally effective method compared to other options such as embryo and oocyte cryopreservation [68,69]. According to ASCO guidelines, GnRHa therapy is recommended when other established fertility preservation methods cannot be implemented in young breast cancer patients [5].

Fertility preservation strategies: conclusion

Breast cancer survivors who become pregnant after cancer treatment have 41% reduced mortality risk compared to those who did not become pregnant; this implies that pregnancy does not negatively impact the prognosis of breast cancer [70]. Therefore, fertility preservation for breast cancer patients must be considered, and breast cancer survivors should not be deprived of the opportunity to become pregnant owing to a lack of understanding and a vague fear of fertility-preserving treatments. Fertility preservation before cancer treatment should be strongly encouraged, considering the fast-developing rate of oncologic treatments, survival rates that are constantly improving, and increased demand for a better quality of life after breast cancer treatment. Still, there are barriers, including those related to the physician, patient, and medical environment including economic support; therefore, we should prioritize eliminating barriers and facilitating shared decision with a multidisciplinary team for appropriate future life decisions. Providing patients with adequate information on fertility preservation at the right time is crucial. An early referral to a fertility specialist in a gynecological clinic serves as the key step to the success of fertility preservation.

ONCOFERTILITY STRATEGIES

Oncofertility is a term that refers to urgent and unmet need of young patients with cancer who are candidates for receiving life-saving but fertility-threatening therapies. Oncofertility counseling represents a crucial step to informing patients with cancer of the risk of developing treatment-induced premature ovarian failure and infertility, based on the proposed anticancer therapies, and involves the presentation of different available options to preserve ovarian function and fertility through discussion of the pros and cons of each option [71].

However, breast cancer patients have a lower birth rate than other cancer patients as well as the general population [72]. Younger patients with breast cancer often have more biologically aggressive tumor characteristics than older patients and tend to receive more chemotherapy and a longer duration of endocrine therapy [73]. Breast cancer treatment can affect fertility directly via gonadotoxic chemotherapy and indirectly through an age-related decline in the ovarian reserve as patients complete their therapy [74-77]. For patients with hormone receptor positive tumors, standard endocrine therapy requires tamoxifen for at least 5 or even 10 years and/or 2 to 5 years of ovarian suppression [78]. Due to the long treatment period, fertility rates will be decreased with increasing age of patients after completion of treatment [79]. The negative impact of anticancer therapies on gonadal function and the success rate of available fertility preservation options are strongly linked to the patient's age and gonadal reserve. The risk of treatment-related infertility can be difficult to estimate because of limited

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available data. It is important to consider the risk in patients; and providers should be careful not to over or under-estimate the risk of treatment-related ovarian failure and infertility and the risk of breast cancer for individuals.

More than 50% of patients with breast cancer of childbearing age have concerns about treatment-related early menopause or infertility [80]. These fertility concerns can also lead to problems with treatment adherence [4], and unplanned non-adherence is related to low survival rates [81]. In some patients with very low risk of relapse, forgoing treatment or reducing the duration of endocrine treatment may be the alternative option. However, this option should include an oncofertility plan before starting treatment.

BARRIERS TO FERTILITY PRESERVATION TREATMENT

Over the past years, growing attention has been given to maintaining fertility and future reproductive potential in young women with cancer [71]. Despite developing a special program to support clinicians in oncofertility counseling [82,83], several barriers to discussing these issues result in subsequent limited access to fertility preservation procedures and a low percentage of breast cancer survivors who achieve a pregnancy [71].

Physician's barriers

Partridge et al. [80] reported that 27% of patients discussed fertility issues with their physician while 81% did not discuss with a specialist. Female doctors and physicians with sufficient knowledge scores and favorable attitudes toward fertility preservation, intend to discuss more and do more consultation and referrals [84]. A survey study for medical oncologists in the United States was conducted among those that were willing to participate in the open POSITIVE trial, which is a single-arm prospective cohort study for women with breast cancer who wanted to get pregnant and among whom antihormonal therapy was interrupted in an attempt to get pregnant [85,86]. It means that the oncologist who participated in this survey had a positive attitude toward fertility. Therefore almost 98% of them answered that they discussed future fertility with patients and referred them to specialists. However, even though the oncologist had a positive attitude toward fertility preservation, 27% of the patients did not want to discuss fertility preservation, 47% mentioned issues with the cost of the procedure, and 26% were concerned about the risk of recurrence. More importantly, 77% still consider that breast cancer treatment is more important than fertility preservation, and 58% responded that patients with poor prognoses should not pursue fertility preservation [86]. Cioffi et al. [87] reported that stage and grade of breast cancer do not impact the number of retrieved mature oocytes, but a higher grade of breast cancer is associated with lower AFC at baseline and the need for a higher dose of gonadotropin during ovarian stimulation [88]. Therefore, discussion of fertility preservation should allow appropriate time for reflection, in trying to eliminate physician's prejudice including on age, ovarian reserve, and risk of breast cancer.

Approximately 5%–10% of breast cancer cases are related to hereditary conditions. In more than 80% of hereditary breast tumors, the responsible genetic abnormality is a germline deleterious mutation in the breast cancer susceptibility genes, BRCA1 or BRCA2 [89]. In BRCA-mutation carriers, breast cancer often occurs during the reproductive age, while ovarian cancer is very rare before the age of 40–45 years [90]. Identifying a deleterious BRCA mutation plays a relevant role in hereditary cancer prevention, diagnosis, and treatment with possible impact on

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these women's reproductive potential. Although for the majority of young women with breast cancer, the information on the BRCA mutational status is not known during the oncofertility counseling and at the time of diagnosis; however, most of them are nowadays candidates to undergo genetic testing [91]. Despite the availability of growing evidence regarding counselling of young women with breast cancer on the safety and efficacy of different strategies for fertility preservation as well as the feasibility of having a pregnancy after diagnosis, numerous challenges persist for patients with BRCA mutations due to both their specific needs and the lack of data on these topics. Whenever available and allowed by national laws and regulations, egg donation and surrogacy represent other potential options for breast cancer patients including those with BRCA mutation. Reproduction studies to address the specific issues of BRCA-mutated breast cancer patients, including the impact of the mutation on their fertility potential, the safety and efficacy of the different strategies for fertility preservation, and the feasibility of having a pregnancy after diagnosis, should be considered a research priority with the final goal to improve the oncofertility counseling of these patients [92].

Patients' barriers

Fertility information is a well-known unmet need among young adult cancer survivors [93]. In addition to the lack of information, decisional conflicts about family planning (FP) arise in complex decision-making processes [94]. The prevalence of high decisional conflict was significantly higher in participants not referred for FP counseling [95]. Therefore, providing necessary information through appropriate referral to reproductive specialists is important in survivorship care of patients in the reproductive age. Treatment delay and oncologic outcomes regarding fertility preservation procedures and pregnancy after cancer are major concerns for patients considering oncofertility decision-making. Shin et al. [96] reported that 44% of patients did not want treatment delay for fertility preservation procedure and 33% of patients only allowed 1 or 2 weeks of treatment delay for the procedure. Therefore, health care providers providing care for young women with breast cancer including medical and surgical oncologists should address the possibility of infertility and ovarian dysfunction as early as possible before treatment start [5].

Increasingly, individuals with cancer are being required to pay a larger proportion of costs according to the national support and insurance coverage. Higher patient costs have been shown to be a barrier to initiating and adhering to the recommended treatment [5,86]. Considering that breast cancer is the most common cancer in childbearing age, and pregnancy rate in young women with breast cancer is low compared with those of women with other cancers, an economic barrier to fertility preservation procedure in young women with breast cancer is a priority to help in patient's decision-making.

Supportive system

In the clinical setting, time constraints are the most frequently reported barriers in FP discussion. This problem has been previously reported in a Korean study, where patients' lack of interest in FP was also reported as a significant part of the barriers [97]. However, the percentage reported for patients that did not want to discuss FP was the lowest (11.2%) of all survey items regarding barriers in our study. Barriers such as time constraints, lack of people to consult with, and poor collaboration with reproductive specialists are systematic barriers that individual physicians' efforts cannot resolve. Kelvin et al. [82] reported that hospital-level cancer and fertility programs resulted in significant improvements in patient satisfaction and helpfulness of information about treatment-related fertility risks and FP options. Therefore, support and establishing programs at the hospital and national level will be needed to overcome

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obstacles and improve fertility-related practices. The study conducted in Japan showed that major barriers to fertility preservation counseling include the risk of recurrence and the medical environment including collaborating with specialists and time constraints [98].

To overcome time constraints and ensure proper counseling, educational material may be helpful in discussing fertility. [99] Shin et al. [96] reported that about half of young women with breast cancer were unaware of the effects of anticancer treatment on ovarian function and fertility, but after viewing educational videos provided by health care professionals, only 2% of patients answered that they had no knowledge. Several FP decision aids for patients with breast cancer have been developed and systemized, and their effectiveness has been proven [82,100]. Therefore, such standardized educational materials and decision aids for FP should be developed and distributed to improve current FP practices. During treatment decision-making for women who are interested in future fertility, it is also crucial to counsel individual patients. A multidisciplinary team including oncology and fertility specialist to improve the referral rates of interested patients for fertility preservation treatment is warranted [101].

PREGNANCY AFTER BREAST CANCER

Around 4.2% of patients become pregnant after treatment of breast cancer [102]. In a meta-analysis comparing patients with breast cancer with the general population, breast cancer survivors were less likely to become pregnant (relative risk, 0.40) [102]. However, the lower pregnancy rate in breast cancer survivors would partly be attributed to the limited fertility window during treatment as well as concerns regarding adverse reproductive outcomes after exposure to chemotherapeutic agents [102,103].

Theoretically, the high estrogen status throughout pregnancy raises concerns about cancer relapse, especially in the hormone receptor-positive breast cancer [11,102]. However, patients with breast cancer who subsequently became pregnant had significantly better disease-free survival (hazard ratio, 0.66) and overall survival (hazard ratio, 0.56) compared to patients who did not, even after correcting for potential confounders, including patient, tumor, and treatment characteristics, pregnancy outcome, and timing of pregnancy [102]. This observation could be attributed to healthy patient bias [102], but there are also some reports indicating that high levels of estriol, the main component of estrogen during pregnancy, may potentially wash out the effect of E2 and estrone on the development of breast cancer [104]. Nevertheless, patients who wish to conceive are recommended to continue using anti-estrogen treatment for at least two years with monitoring of disease recurrence [105]. After confirming that there is no evidence of disease after two years, patients may discontinue the anti-estrogen treatment and try conception. In addition, since tamoxifen is a teratogen, it is recommended that women who are trying to conceive should discontinue tamoxifen for at least three months before attempting pregnancy [103]. Currently, there is an ongoing clinical trial (POSITIVE trial) investigating the impact of temporary endocrine therapy interruption to allow for pregnancy and confirm the safety of pregnancy in breast cancer survivors [85].

The obstetric complication can also be of concern. In the meta-analysis, the breast cancer survivors showed a significantly higher risk of cesarean section (OR, 1.14), low birth weight (OR, 1.50), preterm birth (OR, 1.45), and small for gestational age (OR, 1.16) [102]. However, there were no differences in all other obstetric complications and congenital abnormalities in the child [102].

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In brief, current data support that pregnancy after breast cancer can be considered safe. Even though a multidisciplinary approach to the management of pregnant breast cancer survivors is warranted to achieve the best outcome for these patients.

COMMUNICATING AND DISCUSSING WITH PATIENTS IN DECISION-MAKING

Even though many cancer patients express interest in parenthood, fertility preservation remains relatively scarce [106]. While patients are often unaware of treatment-related infertility, healthcare professionals have insufficient information about fertility issues to provide to breast cancer patients due to low levels of knowledge [94] and unmet needs [93,107]. Physicians also are under pressure and have competing priorities, as well as issues related to reimbursement and collaborative multidisciplinary approaches, which can lead to poor patient-oncologist fertility discussions and delays in referrals [108]. Therefore, it is necessary to improve fertility preservation counseling and clarify what women with cancer consider when making fertility-related decisions. To assist with treatment decision-making, decision aids (educational materials) can be provided to patients who want more information [109]. These interventions increase knowledge and decrease decisional conflict without increasing anxiety [110]. Studies have shown that psychosocial interventions, mostly cognitive behavioral in nature, reduce distress associated with fertility in the general population [111]. However, cancer patients may face stressful situations, including time pressure, to decide whether to preserve fertility, as well as disease-related distress and worries about their suitability for long-term parenthood.

In order to make a fertility decision, participants must consider their values and preferences about having a child. In one study about the decision-making of fertility preservation, the authors defined certainty factors including information or emotional support, and uncertainty factors including time constraints, recurrence risk, labeling, and unmet needs [112]. By receiving the information that they could use to preserve their fertility, healthcare professionals may provide patients with certainty information. Moreover, emotional support from parents and peers helps them to make decisions with greater certainty. Despite this, patients may experience uncertainty when making a decision. Cancer patients feel that they do not have sufficient time to decide on fertility preservation before cancer treatment. The risk of recurrence also makes them reluctant to decide on fertility preservation. Additionally, they may think that they are viewed as typical cancer patients. The patients have many unmet needs and have to make a decision regardless of their lack of understanding about fertility treatment phases and schedules and the risks of cancer therapy and recurrence. This decision-making model showed us that healthcare professionals should provide fertility preservation counseling and timely information, to make participants feel satisfied and confident. Furthermore, since many women with cancer have difficulty verbalizing concerns and asking targeted questions, interventions aimed at improving patients' comprehension of fertility preservation and their sense of support should be considered [113,114].

Furthermore, communication between physicians, patients, and their families regarding fertility preservation is hindered by various barriers, and Jona et al. [115] discussed the barriers. First, the time frame. After a cancer diagnosis, many patients and healthcare professionals are anxious to begin cancer treatment, and fertility preservation discussions are forgotten or only discussed in a short time. Second, the cost. Costs associated with

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fertility preservation are significant, such as cryopreservation, which can cost hundreds to thousands of dollars per year in out-of-pocket storage fees. The result is that some healthcare professionals prevent cancer patients who clearly cannot afford fertility preservation from discussing the procedure, citing ethical dilemmas involved in offering something that they are able to afford. Third, patient characteristics. It might be important to consider the patient's age, the number of children she has, and the stage of cancer development when considering fertility preservation. Fourth, healthcare professionals' role. Healthcare providers are often unaware of information resources concerning fertility preservation and do not provide them to patients. In addition, some oncologists or surgeons may be reluctant to discuss it because they think it falls outside their scope of practice [116] and assume other professionals such as reproductive endocrinologists, obstetricians, and gynecologists should discuss it.

A multidisciplinary team including oncologist, surgeon, endocrinologist, gynecologist, or psychiatrist is appropriate for a better discussion. Specialists in each area can provide the patients with the best information to help them make the best decision for fertility preservation. In particular, psychiatric interviews may be used to assess their level of psychological distress and psychiatric symptoms and investigate the more complex emotional meanings behind their decisions. The patient will also have the opportunity to express her emotion.

CONCLUSION

Breast cancer survivors who become pregnant after cancer treatment have 41% reduced mortality risk compared to those who do not; this implies that pregnancy does not negatively impact the prognosis of breast cancer [70]. Therefore, fertility preservation for breast cancer patients must be considered, and breast cancer survivors should not be deprived of the chance to become pregnant owing to a lack of understanding and a vague fear of fertility-preserving treatments. Fertility preservation before cancer treatment should be strongly encouraged, considering the fast-developing rate of oncologic treatments, survival rates that are constantly improving, and increased demand for a better quality of life after breast cancer treatment. Still, there are barriers, including physician, patient, and medical environment and economic support. Therefore, we should prioritize eliminating barriers and the making of a shared decision-making with a multidisciplinary team for appropriate future life decisions. Providing patients with adequate information on fertility preservation at the right time is crucial. An early referral to a fertility specialist in a gynecological clinic serves as key to the success of fertility preservation.

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