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Fertility preservation for patients with breast cancer: The Korean Society for Fertility Preservation clinical guidelines

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With advances in the methods of cancer treatment used in modern medicine, the number of breast cancer survivors has been consistently rising. As the number of women who wish to become pregnant after being diagnosed with breast cancer increases, it is necessary to consider fertility preservation in these patients. However, medical doctors may be unaware of the importance of fertility preservation among cancer patients because most patients do not share their concerns about fertility with their doctors. Considering the time spent choosing and undergoing treatment, an early referral to a reproductive specialist is the best way to prevent a delay in cancer treatment. Since it is not easy to make decisions on matters related to cancer diagnosis and fertility, patients should be provided with enough time for decision-making, and to allow for this, an early referral will provide patients with sufficient time to choose an appropriate method of fertility preservation. The currently available options of fertility preservation for patients with breast cancer include cryopreservation of embryos, oocytes, and ovarian tissue and gonadotropin-releasing hormone agonist treatment before and during chemotherapy. An appropriate method of fertility preservation must be selected through consultations between individual patients and health professionals and analyses of the pros and cons of different options.

Keywords: Breast neoplasms; Fertility preservation; Pregnancy

Introduction

With advances in the methods of cancer treatment used in modern medicine, the number of cancer survivors has been consistently rising. The Surveillance, Epidemiology, and End Results (SEER) program reported that in 2013, the incidence of breast cancer was 125 cases per 100,000 persons and that the 5-year breast cancer survival rate was 89.7% in the United States [1]. This means that the number of breast cancer survivors in the United States is approximately 3 million. In South Korea, 18,304 people were diagnosed with breast cancer in 2014, which is four times the number recorded 15 years prior. The 5-year relative survival rate was 83.2% in 1996 to 2000, and has increased to 92.0% in 2010 to 2014 [2]. With the increase in the survival rate of breast cancer, it has become important to reduce the rate of postoperative morbidities and to consider cancer survivors' quality of life. Fertility preservation is especially important in Korea, where the number of patients who develop breast cancer before menopause is considerably higher than in the United States (47.9% vs. 20.0% in women aged less than 50 years) [3,4]. We would like to discuss several issues related to fertility preservation in patients with breast cancer that may be important to consider during the treatment of these patients.

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Should patients diagnosed with breast cancer be referred to fertility specialists?

One of the main concerns of young patients with cancer is whether

cancer treatment will affect their fertility. However, oncologists generally remain unaware of the importance of fertility preservation among cancer patients because most patients do not share their concerns about fertility with their doctors. Patients may be too shocked upon learning of their cancer diagnosis to discuss any other matters with their doctors [5]; however, younger women with a diagnosis of breast cancer reported that they had unmet needs for fertility- or menopause-related discussions with a reproductive specialist [6]. Counseling about premature ovarian insufficiency and fertility issues is an overlooked part of the treatment plan for young premenopausal women with breast cancer [7].

Partridge et al. [8], in their study of patients with early breast cancer, reported that 57% of the patients were concerned about their future fertility upon learning of their cancer diagnosis, and 29% responded that their concerns affected their decision with regard to therapy. In addition, 51% of all patients felt that their concerns about fertility were inadequately addressed, indicating that there was insufficient communication between health professionals and the patients. Young women who are interested in fertility preservation should be referred to a fertility specialist as soon as possible, as recommended by several international guidelines [9-11].

What significance does early referral to fertility preservation specialists hold for patients?

Considering the time spent choosing and undergoing treatment, an early referral to a reproductive specialist is the best way to prevent a delay in cancer treatment. An early referral to a fertility specialist can reduce conflicts in decisions about fertility preservation [12].

In a study by Lee et al. [1] conducted on 93 patients with breast cancer, 35 patients were referred to a reproductive specialist before surgery and 58 after surgery. The mean time from the first diagnosis to the initiation of ovarian stimulation was 42.6 days for patients who were referred before surgery and 71.9 days for those who were referred after surgery. In addition, the mean time from the first diagnosis to the first chemotherapy session was 83.9 days for patients who were referred before surgery, and 107.8 days for those who were referred after surgery; the former were able to undergo chemotherapy much earlier than the latter ($p=0.045$). A significant difference in the number of patients who could afford time to undergo two cycles of fertility preservation before treatment was also found; 25.7% of patients referred before surgery and 1.7% of patients referred after surgery were able to undergo fertility preservation twice. As a result, the number of oocytes retrieved increased by 18%. Since it is not easy to make decisions on matters related to cancer diagnosis and fertility, patients should be provided with enough time for decision-making, and to allow for this, early referral to the appropriate health professionals is crucial.

The effects of chemotherapy on fertility

The ovarian dysfunction following chemotherapy in patients with malignant tumors is affected by the patient's age, ovulatory function at the time of treatment, the type of medications used, and the length of treatment. Alkylating agents such as cyclophosphamide and ifosfamide have an especially high risk for ovarian failure, while antimetabolites pose a relatively low risk [13]. The average rate of chemotherapy-related amenorrhea was 30% to 40% in in women aged less than 40 years and 76% to 95% in women aged 40 or more years after cyclophosphamide, methotrexate, and 5-fluorouracil treatment for at least 3 months [14,15]. In contrast, four cycles of anthracycline and cyclophosphamide and paclitaxel led to amenorrhea in 13.5% of women younger than 40 years, but 69.9% of women aged 40 to 49 years [16]. Furthermore, there was no difference in amenorrhea according to trastuzumab use in patients with human epidermal growth factor receptor 2-positive breast cancer [16].

In many cases, it is difficult to clearly assess the effects of chemotherapy on fertility. This is because amenorrhea does not necessarily indicate menopause and it is experienced by patients with female-hormone dependent cancer following the administration of tamoxifen, making it difficult to tell whether a patient has reached menopause or not [17,18]. Furthermore, even when a patient menstruates regularly, it cannot be concluded that chemotherapy has had no effect on her ovulatory function. All of these considerations must be taken into account when conducting research on the effects of chemotherapy on fertility and the prevention of these effects. To overcome these limitations, ovulatory function must be assessed using anti-Müllerian hormone, follicle-stimulating hormone, and ultrasonography in addition to checking the patient's menstrual status.

What options are available for patients with breast cancer who wish to preserve their fertility?

Patients with breast cancer who wish to preserve their fertility may choose to undergo oocyte or embryo cryopreservation, cryopreservation of ovarian tissue that is obtained before the administration of anticancer drugs, or suppression of the effects of anticancer drugs on the ovaries through ovarian suppression.

1. Embryo or oocyte cryopreservation

Embryo cryopreservation is the most well-established method of fertility preservation. Embryo cryopreservation follows the procedure used in infertile patients for *in vitro* fertilization. The ovaries are stimulated with gonadotropic hormones to acquire multiple oocytes, and then gonadotropin-releasing hormone (GnRH) agonists or antago-

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nists are administered to inhibit early ovulation. After 30 years of being clinically practiced, *in vitro* fertilization has now become a standardized procedure, alongside embryo cryopreservation, which has also been widely used as a method of preserving surplus embryos. However, for *in vitro* fertilization, drug administration starts during the early proliferative phase of the menstrual cycle, and cancer patients may find it difficult to wait for the optimal timing. Although luteolysis has been suggested to induce early menstruation, cryopreservation is only indicated for a small number of patients.

However, since the recent discovery that follicle recruitment occurs multiple times within a single menstrual cycle [19], ovarian stimulation has been performed regardless of timing within the menstrual cycle (random-start protocol). It has also been reported that luteal-phase ovarian stimulation, which was considered inadequate in the past, does not affect the number of oocytes retrieved [20,21]. Since oocyte retrieval typically takes around 2 weeks, a patient can be offered a wide variety of options for fertility preservation if she can afford 2 to 3 weeks of waiting time.

For fertility preservation in postpubertal females without a committed male partner, oocyte cryopreservation is another option for fertility preservation [22]. Even if the protocol for ovarian stimulation and oocyte retrieval in oocyte cryopreservation is similar to that of embryo cryopreservation, concerns have been articulated regarding lower implantation and pregnancy rates than those obtained with fresh or frozen embryos. However, recent studies have reported that embryo transfer cycles using frozen-thawed oocytes had comparable success rates to those using unfrozen oocytes [23-25]. As cryopreservation and thawing techniques have been refined recently, oocyte cryopreservation is no longer considered experimental [22].

A supraphysiologic level of estradiol during fertility preservation, including controlled ovarian stimulation (COS), might stimulate the proliferation of breast cancer cells. Therefore, a modification of conventional COS protocol has been developed to prevent this potential harm. Administration of letrozole as an aromatase inhibitor before and after ovarian stimulation seems to be a feasible option [26-31]. The co-administration of letrozole is effective in reducing the peak estradiol level without a decrease in oocyte yield [26,31]. Although definitive large-scale trials regarding the safety of COS in women with breast cancer do not yet exist, the largest prospective study [28] reported that recurrence after COS was comparable to controls and that the survival rate was not compromised. Moreover, a recent cohort study including 3,136 natural cycles and 792 letrozole cycles reported that there was no increase of major congenital malformations in women treated with letrozole for COS compared with women who underwent natural cycles [32].

2. Ovarian tissue cryopreservation

Tissue cryopreservation of the ovarian cortex seems to be an efficient way of preserving ovarian function, at least theoretically. In ovarian tissue cryopreservation, ovarian tissue is resected prior to chemotherapy, cryopreserved, and retransplanted upon treatment completion. Depending on the part of the tissue to be removed, a cortical strip or the whole ovary may be resected, and depending on the location of the transplant, orthotopic or heterotropic transplantation may be performed. More than 60 live births have been reported from ovaries cryopreserved with slow freezing or vitrification [33] though ovarian tissue cryopreservation still should be considered experimental.

During the process of freezing and thawing, ischemia of the ovarian tissue may occur, which can lead to loss of a substantial number of primordial follicles. Thus, cryopreservation and thawing by experienced hands is important, and the transplantation technique is also important for reducing ischemic damage. In patients with malignant tumors, a histologic examination or other possible tests such as polymerase chain reaction and xenotransplantation of a part of the tissue should be considered to check whether the malignant tumor has spread to the preserved ovarian tissue. Since metastasis of breast cancer to the ovary is not an extraordinary event in the course of breast cancer [34,35], patients should be informed about this probability. For patients at increased risk of ovarian cancer due to comorbid diseases closely associated with genetic mutations such as *BRCA1* and *BRCA2*, removal of the transplanted ovarian tissue and oocyte donation can be considered upon completion of successful pregnancy and delivery.

3. Inhibition of ovarian function using GnRH agonists

The mechanism by which GnRH agonists preserve ovarian function is still not clear. Possible hypotheses are that GnRH agonists inhibit follicle-stimulating hormone secretion, shorten the ovarian and uterine cycles, inhibit the activation of GnRH receptors, and inhibit the upregulation of intragonadal antiapoptotic molecules [36]. In addition to embryo, oocyte, or ovarian tissue cryopreservation, which are performed before gonadotoxic therapy, a GnRH agonist can be used during chemotherapy. Although the effectiveness of GnRH agonists remains controversial, several studies have found that they led to a significant reduction of the risk of ovarian failure [37,38]. Moreover, a higher rate of resuming menstruation and a higher probability of pregnancy in patients undergoing GnRH agonist co-administration was demonstrated in a recent meta-analysis [39-41]. Although the evidence from these recent studies can be reasonably interpreted to support using a GnRH agonist during chemotherapy in women with breast cancer, GnRH agonist therapy cannot replace established methods of fertility preservation, such as embryo, oocyte, or ovarian

tissue cryopreservation. Clinicians should discuss these issues with patients with breast cancer before the use of a GnRH agonist during chemotherapy.

Fertility preservation in women undergoing neoadjuvant chemotherapy

As described, oocyte or embryo cryopreservation is well established as a fertility preservation strategy, and a random-start protocol can shorten the duration of COS. However, concerns have been raised that oocyte or embryo cryopreservation might delay treatment among patients undergoing neoadjuvant chemotherapy because most of these patients have a more aggressive form of disease, making chemotherapy more urgent [42]. Although a recent small study reported that the initiation of systemic therapy was not delayed in women receiving COS before neoadjuvant chemotherapy [42], these issues of fertility preservation should be handled in an individualized manner, and the possible benefits and risks should be discussed with all women who undergo neoadjuvant chemotherapy.

Is the fertility of patients who undergo *in vitro* fertilization affected?

While there are concerns about reduced ovarian function in patients with cancer following *in vitro* fertilization, a recent study reported no significant change in ovarian function [43]. Concerns have also been raised that the increased level of estrogen after ovarian stimulation performed in preparation for *in vitro* fertilization may affect the prognosis of female-hormone dependent cancers, such as breast cancer. The administration of tamoxifen or an aromatase inhibitor before and after ovarian stimulation has been shown to significantly lower the level of estrogen, without affecting the fertilization rate [44] or the recurrence rate of breast cancer [45].

Conclusion

The currently available methods of fertility preservation for patients with breast cancer include cryopreservation of embryos, oocytes, and ovarian tissue and GnRH agonist treatment during chemotherapy. An appropriate method of fertility preservation must be selected based on consultations between individual patients and health professionals and analyses of the pros and cons of different options. Most importantly, patients should be promptly referred to fertility specialists upon receiving a cancer diagnosis. An early referral will allow patients sufficient time to choose an appropriate method of fertility preservation.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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