FERTILITY PRESERVATION IN YOUNG WOMEN WITH EARLY-STAGE BREAST CANCER

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SUMMARY – Although breast cancer (BC) occurs more often in older women, it is the most commonly diagnosed malignancy in women of childbearing age. Owing to the overall advancement of modern medicine and the growing global trend of delaying childbirth until later age, we find ever more young women diagnosed and treated for BC who have not yet completed their family. Therefore, fertility preservation has emerged as a very important quality of life issue for young BC survivors.

This paper reviews currently available options for fertility preservation in young women with early-stage BC and highlights the importance of a multidisciplinary approach to fertility preservation as a very important quality of life issue for young BC survivors. Pregnancy after BC treatment is considered not to be associated with an increased risk of BC recurrence; therefore, it should not be discouraged for those women who want to achieve pregnancy after oncologic treatment. Currently, it is recommended to delay pregnancy for at least 2 years after BC diagnosis, when the risk of recurrence is highest. However, BC patients of reproductive age should be informed about the potential negative effects of oncologic therapy on fertility, as well as on the fertility preservation options available, and if interested in fertility preservation, they should be promptly referred to a reproductive specialist. Early referral to a reproductive specialist is an important factor that increases the likelihood of successful fertility preservation. Embryo and mature oocyte cryopreservation are currently the only established fertility preservation methods but they require ovarian stimulation (OS), which delays initiation of chemotherapy for at least 2 weeks. Controlled OS does not seem to increase the risk of BC recurrence. Other fertility preservation methods (ovarian tissue cryopreservation, cryopreservation of immature oocytes and ovarian suppression with gonadotropin-releasing hormone agonists) do not require OS but are still considered to be experimental techniques for fertility preservation.

Key words: Fertility preservation – methods; Breast neoplasms; Cryopreservation – methods; Ovulation, induction; Gonadotropin-releasing hormone – agonists; Quality of Life

Introduction

Although the incidence of breast cancer (BC) increases with age, it is the most commonly diagnosed malignancy in women of childbearing age with 10.5% of new cases diagnosed every year in patients younger than 45 years1. Younger women present more often with more aggressive BC requiring gonadotoxic che-
motherapy and subsequently endocrine therapy for hormone receptor (HR)-positive BC, which can significantly impair fertility\(^2\). Advances in BC awareness, early detection, diagnosis and treatment options have increased BC survival rates. Because of the global trend of delayed childbearing, there is a growing population of young women diagnosed with BC before they have completed their family\(^3\).

Data show that at the time of diagnosis, approximately 50% of young women are concerned about becoming infertile after BC treatment, but only a minority (10%) used fertility preservation strategies\(^4\). Therefore, fertility preservation in young BC patients has emerged as a very important survivorship issue regarding the quality of life for these women and it should be discussed early upon diagnosis with all BC patients of reproductive age. A recent meta-analysis showed that BC survivors who had received adjuvant systemic therapy for BC had a 14% chance of becoming pregnant with the pregnancy rate by 40% lower than the pregnancy rate in the general population.\(^5\)

Therefore, BC patients of reproductive age should be informed about the potential negative effects of oncologic therapy on fertility and fertility preservation options, and delay of cancer treatment\(^6,9\). Early referral gives young BC patients a chance to undergo multiple cycles of embryo/oocyte cryopreservation if desired, which increases the chance of successful fertility preservation because of the increased number of embryos/oocytes stored.\(^10\)

Factors Influencing Fertility Preservation

Young women interested in fertility preservation should be referred to a reproductive specialist as soon as possible. Several factors should be discussed with BC patients who are faced with gonadotoxic therapy, i.e. type of cancer, patient age, reproductive history, comorbidities, type, dose, expected benefits and adverse effects (AE) of planned oncologic therapy, need for endocrine therapy, risk of infertility after planned oncologic treatment, fertility preservation options, and delay of cancer treatment\(^6,9\). Early referral gives young BC patients a chance to undergo multiple cycles of embryo/oocyte cryopreservation if desired, which increases the chance of successful fertility preservation because of the increased number of embryos/oocytes stored.\(^10\)

Early referral to reproductive center before surgery allows women who will undergo OS and fertility preservation to start adjuvant chemotherapy around 3 weeks earlier than those women who were referred after surgery\(^11\). Chemotherapy-induced ovarian damage depends on the patient age at BC diagnosis, individual ovarian reserve, and type and dose of planned chemotherapy. The risk of ovarian failure is greater in older patients, especially in patients older than 40 years, even at lower doses of gonadotoxic chemotherapy, primarily due to natural reduction in the number of primordial follicles that comes with aging.\(^12,13\). Chemotherapeutic agents can cause damage to developing follicles because granulosa cells are proliferating cells and therefore cause transient amenorrhea. Induced ovarian damage is associated with a reduction in the follicle number, follicular apoptosis, damage to ovarian stroma, impaired blood flow, and increased follicular recruitment.\(^12\) Alkylating agents cause deoxyribonucleic acid (DNA) double-strand breaks and they are considered to be the most gonadotoxic chemotherapeutic agents. As alkylating agents are non-cell-cycle specific, they can cause damage to both resting and growing follicles.\(^12,13\)

The dose of chemotherapy is also an important factor. The CMF (cyclophosphamide, methotrexate, 5-fluorouracil) protocol seems to be more gonadotoxic than the AC (doxorubicin, cyclophosphamide) protocol, probably because of a higher cumulative dose of cyclophosphamide reached with CMF compared to AC protocol.\(^14\) Significantly lower rates of amenorrhea (34% vs. 69%) have been reported with the AC protocol com-
pared to CMF protocol\(^\text{15}\). It has been reported that chemotherapy protocols such as AC may result in a 10-year loss of oocyte reserve\(^\text{16}\). The addition of taxane and trastuzumab to AC protocol or dose-dense approach did not seem to significantly increase the risk of amenorrhea compared to AC protocol\(^\text{17}\). An update from a single arm adjuvant paclitaxel-trastuzumab (APT) study showed a lower amenorrhea rate (28\% vs. 95\% CI; 18\%–41\%) among premenopausal women treated with adjuvant paclitaxel and trastuzumab compared to standard BC regimens with alkylating agent\(^\text{18}\).

Furthermore, surgeons, radiologists and psychosocial providers should be informed about this important issue and included in the management of BC patients. Early referral to a multidisciplinary team offers selection of the most required fertility preservation method for fertility preservation, between the standard methods such as embryo or oocyte cryopreservation and experimental options including ovarian tissue cryopreservation, cryopreservation of immature oocytes and ovarian suppression with gonadotropin-releasing hormone agonists (GnRHa)\(^\text{19}\). An overview of available fertility preservation methods, including their advantages and disadvantages, is shown in Table 1.

### Embryo Cryopreservation

Embryo cryopreservation is the most established fertility preservation method for BC patients who have male partners, or for those women who are using...
donor sperm, but it has several ethical and legal concerns such as prohibition of this method in some countries, posthumous reproduction or divorce. This method combines ovarian stimulation (OS), oocyte retrieval and in vitro fertilization (IVF). The success of this method is highly dependent on the number of stored oocytes or embryos and patient age. OS with gonadotropins is needed to gain more than one oocyte per cycle and it is very important for successful IVF, especially because most BC patients usually have only one opportunity to undergo IVF protocol before starting gonadotoxic treatment. Controlled OS for fertility preservation is considered not to be associated with an increased risk of BC recurrence. The process of embryo cryopreservation delays oncologic treatment for 2 to 5 weeks, therefore, it is not recommended for patients who cannot delay BC treatment.

In order to reduce the risk of short-term exposure to very high estrogen levels in BC patients, alternative and safer protocols for OS using aromatase inhibitors and tamoxifen with gonadotropins have been developed to reduce estrogen production. The preferred option for OS in fertility preservation cycles for women with HR-positive BC are stimulation protocols using letrozole with gonadotropins because they are safe, more effective than tamoxifen protocols, and are associated with a higher number of oocytes retrieved and fertilized. Use of these protocols resulted in overall live birth per embryo transfer of 45%, which is comparable to those in a non-cancer population undergoing IVF because of infertility.

Random-start OS protocols for emergency fertility preservation are initiated in the late follicular or luteal phase of the menstrual cycle and they allow OS to start anytime during the menstrual cycle. Random-start protocols have shown to be efficient for fertility preservation with similar numbers of retrieved oocytes, mature oocyte yield, and fertilization rates. With the use of these protocols, there is no need to wait for the onset of the next menstrual cycle because they reduce the waiting period for egg retrieval to about 2 weeks, which allows earlier start of oncologic treatment.

Double OS protocols are developed to allow double stimulation in both follicular and luteal phase of the same menstrual cycle in order to increase the number of obtained oocytes with subsequent improvement in birth rate, without delaying cancer treatment. These protocols could be suitable for patients of advanced maternal age and reduced ovarian reserve but they need to be further investigated.

Oocyte Cryopreservation

Oocyte cryopreservation is an alternative method to embryo cryopreservation for those women without a partner or those who do not want to use donor sperm and in the countries where embryo cryopreservation is forbidden by law. This technique also requires controlled OS and oocyte retrieval, thus having the same disadvantages as embryo cryopreservation. Vitrification has significantly improved live birth rates, with a higher live birth rate reported for women younger than 35 years (live birth rate 50% vs. 22.9% in women older than 36 years).

Cryopreservation of Immature Oocytes

Cryopreservation of immature oocytes or oocytes matured in vitro is a promising experimental fertility preservation option for BC patients. This method is menstrual cycle independent, does not require OS, although short OS lasting for 3–5 days can be performed, which will result in a shortened period from BC diagnosis to initiation of cancer treatment. Upon retrieval, immature oocytes can be either cryopreserved after in vitro maturation or cryopreserved at the immature stage and matured in vitro after thaw. In vitro maturation (IVM) before cryopreservation is reported to be a better option because it results in higher maturation and survival rates than post-thaw maturation (63.8% vs. 33.3%, p<0.05). Data from studies using IVM oocytes are still limited, the implantation and pregnancy rates are significantly lower than with standard IVF, the use of this method should be considered experimental, and it should be performed only in specialized centers.

Ovarian Tissue Cryopreservation

Ovarian tissue cryopreservation (OTC) is an experimental fertility preservation method in which the ovarian cortex, which contains a lot of primordial follicles, is removed surgically and then cryopreserved. Upon completion of oncologic treatment, the ovarian tissue can be thawed and transplanted back into the patient, either to orthotopic (into the pelvic cavity; on the atrophic ovary, pelvic peritoneum) or heterotopic sites (outside of the pelvis; subcutaneous regions such as the forearm, abdominal wall).
This method has several advantages, i.e. it can be performed at any time during the menstrual cycle, there is no need for OS, it does not require delay in the initiation of oncologic treatment or male partner/sperm donor, it results in storage of a large number of primordial follicles and restores endocrine function\textsuperscript{34,35}. OTC is an option for those BC patients who require immediate start of gonadotoxic therapy and do not have enough time to undergo OS for embryo/oocyte cryopreservation. After reimplantation, ovarian function is expected to be recovered after 4-5 months in the majority of cases, and ovarian function is restored in more than 90% of patients with the mean duration of ovarian function after reimplantation of 4-5 years\textsuperscript{36}. Several factors can affect ovarian graft longevity, including advanced age at the time of OTC, previous chemotherapy exposure, graft size and method of cryopreservation, inhomogeneous distribution of follicles in ovarian graft, and post-transplantation ischemia\textsuperscript{36}. Age is an important factor that should be taken into account because the success of OTC is highly dependent on ovarian reserve, which decreases with age. Suggested selection criteria for OTC are age younger than 35 years, a realistic chance of 5-year survival, and at least 50% risk of premature ovarian insufficiency\textsuperscript{34}. Post-transplantation ischemia can cause high follicular loss after transplantation (up to 70% of follicles)\textsuperscript{37}. It is desirable to retrieve ovarian tissue for cryopreservation before initiation of gonadotoxic treatment, but this method can be performed in those young women who normally have a high number of primordial follicles in their ovaries and have already started chemotherapy\textsuperscript{38}. The reported live birth and ongoing pregnancy rate of 37.7% for OTC with endocrine restoration rate of 63.9% has reached promising levels\textsuperscript{39}. It is also suggested that a combination of oocyte vitrification and OTC could increase the live birth rate to 50%-60\textsuperscript{34}. Only one (twin) pregnancy has been reported when ovarian tissue was transplanted to a heterotopic site\textsuperscript{35}. The greatest concern about this method is safety of the procedure because for fear of potential reimplantation of malignant cells, mostly in patients with hematologic malignancies. Ovarian tissue should be appropriately examined (histology, immunohistochemistry, polymerase chain reaction) to exclude malignant involvement of ovarian tissue in cancer patients undergoing OTC\textsuperscript{35}.

When there is a risk of transferring malignant cells, ovarian follicles can be isolated and matured \textit{in vitro}, and then fertilized and transferred to the patient. Another option is the formation of an artificial ovary where isolated follicles are encapsulated into a scaffold, which allows them to grow and develop in an ovarian-like environment and to be grafted to the patient\textsuperscript{34}. Additional potential improvements of this method could be the use of robotic surgery and protective agents such as AS101 or sphingosine-1-phosphate (S1P)\textsuperscript{34}.

**Ovarian Suppression with Gonadotropin-Releasing Hormone Agonists**

Administration of GnRHa is an attractive option for fertility preservation in BC patients because it is noninvasive, easy to administer, does not require the usage of assisted reproductive technologies, and does not require delay in chemotherapy initiation\textsuperscript{9}. Because of a flare effect at the beginning of the treatment with GnRHa, which lasts for about one week, GnRHa should be administered at least one week before chemotherapy. The idea for the usage of GnRHa ensued from the hypothesis that induced gonadal quiescence during chemotherapy could reduce chemotherapy-induced damage\textsuperscript{41}. There are several possible mechanisms of ovarian protection with the usage of GnRHa, including decreased ovarian perfusion and delivery of chemotherapy to the ovaries, prevention of the increased recruitment of primordial follicles by the increased follicle stimulating hormone (FSH) concentration induced through apoptosis of the growing follicles, up-regulation of antiapoptotic pathways within the ovary and protection of ovarian germline stem cells\textsuperscript{42}. More advanced follicles are gonadotropin-responsive and they secrete growth factors (such as TGF-\(\beta\), BMP, activin) that cause growth of primordial and primary follicles. Burnout theory suggests that the gonadotoxic effect of chemotherapy leads to increased concentration of FSH because it causes death of the follicles and decreased levels of estrogen and inhibin. GnRHa decreases FSH levels; therefore, it could cause decreased recruitment of primordial follicles\textsuperscript{43}. On the other hand, primordial follicles do not express gonadotropin receptors; therefore, GnRHa cannot have a direct effect on ovarian reserve\textsuperscript{44}. 
The usage of GnRH agonist in fertility preservation is still considered experimental. Although a recent meta-analysis has suggested that GnRHa reduces the risk of premature ovarian failure (adjusted OR 0.38; 95% CI, 0.26-0.57; p<0.001), the data need to be further investigated. The majority of clinical studies that showed benefit from GnRHa used amenorrhea as a primary outcome, which is an inappropriate surrogate for ovarian function and reproductive potential. Ovarian reserve might be severely diminished despite the resumption of menstruation and those women are more likely to develop early menopause. Also, young non-menstruating women may still be fertile despite the low ovarian reserve because of the high quality of the remaining oocytes. Other limitations of GnRHa studies were the lack of randomization and appropriate controls, retrospective design of studies, and limited long-term data.

The best primary outcome for fertility preservation is successful pregnancy. Although the number of pregnant patients in a recent meta-analysis was relatively small (37 pregnancies in patients treated with GnRHa (10.5%) vs. 20 pregnancies in control group (5.5%), incidence rate ratio 1.83; 95% CI, 1.06-3.15; p=0.030), it suggests a higher chance for pregnancy with the use of GnRHa.

Besides pregnancy rate, fertility preservation can be assessed through ovarian reserve biomarkers such as antimüllerian hormone (AMH), inhibin B levels, or antral follicle count. AMH is considered to be the most sensitive marker of ovarian reserve as it is produced by granulosa cells of primary follicles and is involved in the regulation of primordial follicle recruitment. Decreased AMH levels are associated with diminished ovarian reserve following chemotherapy. A meta-analysis which included 10 trials where ovarian reserve parameters including AMH were evaluated showed no benefit from GnRHa treatment.

Other Noninvasive Fertility Preservation Strategies

Usage of new fetoprotective agents could protect ovaries from chemotherapy-induced damage. Burnout theory suggests that the gonadotoxic effect of chemotherapy leads to activation of dormant follicle growth. Co-administration of the AS101 immunomodulator acts on the PI3K/PTEN/Akt pathway, which is important in the activation of dormant follicles. AS101 prevents follicle activation, which leads to reduced follicular loss and improved reproductive outcomes in mice treated with cyclophosphamide. AMH is also important in the regulation of follicle activation as an inhibitor of recruitment of primordial follicles. The use of recombinant human AMH showed reduced preclinical follicle loss. S1P is a ceramide-induced apoptotic inhibitor, which can prevent chemotherapy-induced apoptotic follicle loss in preclinical models, as well as imatinib and granulocyte colony-stimulating factor (G-CSF). Although these agents are promising noninvasive strategies for fertility preservation, it is important to note that the major concern for clinical usage of these agents is the potential interaction with oncologic treatments and reduced therapeutic effects.

Neoadjuvant Chemotherapy and Fertility Preservation

Young BC patients are often candidates for neoadjuvant chemotherapy because they present more often with larger, node-positive tumors and more aggressive disease (triple-negative, Her-2 positive BC). In neoadjuvant setting there is a desire to start oncologic treatment as soon as possible, but there are several obstacles that are delaying this process such as referral time to oncology specialists, additional oncology consultation, additional diagnostic work-up (MRI, additional biopsies, staging scans, echocardiogram). In the meantime, patients could also have the opportunity to see a reproductive specialist, discuss their fertility preservation options, and if desired undergo fertility preservation.

There is a concern regarding delay and safety of OS in neoadjuvant settings and its potential influence on tumor growth and spread. Random-start protocols with letrozol do not seem to increase the risk of BC recurrence, but reduce the risk of short-term exposure.
to very high estrogen levels, allow earlier start of anticancer treatment by reducing the waiting period for egg retrieval, and can be performed in neoadjuvant settings as long as there is prompt referral\textsuperscript{27,28,52}. There is the need to further evaluate safety of the established fertility preservation methods in the neoadjuvant setting. The neoadjuvant setting is a good setting for still experimental fertility preservation methods such as OTC and cryopreservation of immature ovarian cells because these methods do not require delay in the initiation of oncologic treatment\textsuperscript{13}. Good collaboration among medical oncologists, surgeons and reproductive specialists is crucial for successful fertility preservation, especially in a neoadjuvant setting.

BRCA Mutations and Fertility Preservation

Women carrying BRCA1 and BRCA2 mutations have an increased lifetime risk of developing BC, contralateral BC, and ovarian cancer. A recent prospective study reported the lifetime risk of BC to be around 70% for BRCA1 and BRCA2 carriers, and lifetime risk of ovarian cancer to be 44% for BRCA1 and 17% for BRCA2 carriers\textsuperscript{53}. By the age of 40, the reported cumulative risk of BC development is 24% for BRCA1 and 13% for BRCA2 carriers, while the cumulative risk of ovarian cancer is 2% for BRCA1 and 0% for BRCA2 carriers\textsuperscript{53}. Women with BRCA1/2 mutation are advised to undergo bilateral salpingo-oophorectomy before age 35-40, after they have completed childbearing to reduce the risk of developing ovarian cancer and BC\textsuperscript{54}.

Data suggest that BRCA mutation carriers may have reduced reproductive potential, i.e. diminished ovarian reserve, lower AMH levels, poorer response to controlled ovarian stimulation with letrozole protocols, more pronounced in women with BRCA1 mutation\textsuperscript{55-57}. It is also reported that BRCA1/2 mutation carriers are more likely to experience earlier natural menopause, approximately 3-4 years earlier than healthy women\textsuperscript{58}. Gonadotoxic effects of chemotherapy may be more pronounced in BC patients with BRCA 1/2 mutation, as deficient homologous-recombination DNA repair makes oocytes of these women more vulnerable to gonadotoxic therapy\textsuperscript{59}. Taking into consideration the potentially reduced ovarian reserve in BC patients with BRCA1/2 mutations, using double OS protocols may be useful\textsuperscript{59,60}. Another option for fertility preservation in BC patients with BRCA1/2 mutation is OTC, although there is a safety concern because of the risk of developing ovarian cancer\textsuperscript{51,59}. Heterotopic OTC may be the preferred option for those women because it allows closer monitoring of ovarian tissue\textsuperscript{56}. BRCA1/2 mutations are inherited in an autosomal dominant fashion, so there is a 50% risk of transmission of the mutated gene to the patient’s offspring. Preimplantation genetic diagnosis for BRCA mutation during IVF can be performed to avoid mutation transmission to the embryo, although this is ethically questionable because BRCA mutations are not lethal mutations and their presence does not guarantee cancer occurrence\textsuperscript{16,59,60}. Egg donation and surrogacy are the possible options for women harboring BRCA mutations in countries where those options are available and legal.

Conclusions

Fertility preservation is an emerging field in oncology that gives an opportunity for young cancer survivors to maintain reproductive health and have children after oncologic treatment. Pregnancy after BC treatment does not seem to increase the risk of BC recurrence. Unfortunately, fertility preservation is an under-discussed issue in young BC patients, which should be discussed with every woman of reproductive age diagnosed with early-stage BC and the women interested in fertility preservation should be promptly referred to fertility specialists before starting gonadotoxic therapy. Early referral to a reproductive specialist is a crucial component of fertility preservation, which increases the chance for successful fertility preservation. Good collaboration among specialists included in the management of these patients may increase the likelihood of successful fertility preservation. Currently, embryo and oocyte cryopreservation are safe, effective and well-established options for fertility preservation in BC survivors, whereas other methods, although promising, are still considered to be experimental and controversial, and need to be further investigated.

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Sažetak

OČUVANJE PLODNOSTI U MLADIH ŽENA S RANIM RAKOM DOJKE

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Premda se karcinom dojke češće javlja u starijoj životnoj dobi, to je i najučestaliji malignitet u žena reproduktivne dobi. Zbog sveukupnog napretka modernoj medicini i rastućeg globalnog trenda odgađanja rađanja djece za kasniju dob suočavamo se sa sve više mladih žena s dijagnostičkim i liječenim karcinomom dojke koje još nisu kompletirale obitelj. Stoga je područje očuvanja plodnosti postalo jako bitno u očuvanju kvalitete života mladih žena koje su preboljele karcinom dojke. Ovaj rad iznosi trenutno dostupne metode za očuvanje plodnosti u mladih žena s ranim karcinomom dojke i ističe važnost multidisciplinarnog pristupa u očuvanju plodnosti kao bitnog čimbenika kvalitete života tih žena. Smatra se da trudnoća nakon karcinoma dojke nije povezana s povišenim rizikom od recidiva pa stoga ne treba obeshrabriti žene koje žele ostvariti trudnoću nakon provedenog onkološkog liječenja. Danas se preporuča pričekati s trudnoćom barem 2 godine nakon postavljenih dijagnoza za vrijeme kada je rizik od povrata bolesti najveći. No, isto tako bi bolesnice reproduktivne dobi trebalo obavijestiti o mogućem negativnom učinku onkološke terapije na plodnost te o dostupnim metodama očuvanja plodnosti i u slučaju zainteresiranosti za očuvanje plodnosti bolesnice treba žurno uputiti reproduktivnom specijalistu. Rano upućivanje reproduktivnom specijalistu je bitan čimbenik koji povećava izglede za uspješno očuvanje plodnosti. Krioprezervacija embrija i zerlih oocita su trenutno jedine standardne metode očuvanja plodnosti koje zahtijevaju stimulaciju ovarija kojom se odgaja početak kemoterapijskog liječenja barem 2 tjedna. Smatra se da kontrolirana stimulacija ovarija ne povećava rizik od povrata karcinoma dojke. Druge metode očuvanja plodnosti (krioprezervacija tkiva jajnika, krioprezervacija nezrelih oocita, ovarijska supresija GnRH agonistima) ne zahtijevaju primjenu ovarijske stimulacije, ali se i dalje smatraju eksperimentalnim metodama za očuvanje plodnosti.

Ključne riječi: Plodnost, očuvanje – metode; Dojka, tumori; Kriokonzerviranje – metode; Ovułacija, indukcija; Gonadotropin-otpuštajući hormon – agoništi; Kvaliteta života