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Provision of Fertility Preservation for Young Women with Early-Stage Breast Cancer

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Abstract

Breast cancer is the most common cancer in women worldwide, constituting 25% of all cancer diagnoses. Even though it is only affecting 4% - 6% of women under the age of 40, it remains the most common malignancy among younger patients. Advancement in the treatment and earlier detection gives excellent 5 years of survival. However, the standard treatment that comprises surgical-chemo radiation therapy or hormonal treatment often results in an increased incidence of treatment-induced infertility. Therefore, adding fertility preservation to primary cancer treatment may offer the best opportunity for future fertility. However, despite advancements in Assisted Reproductive Technology (ART), the uptake of fertility services in this group remains low. In this review, we highlighted the effect of all breast cancer treatments on women's fertility, the effectiveness and safety of ART in breast cancer patients as well as the safety of pregnancy in breast cancer survivors. Our aim is to improve awareness of fertility preservation for breast cancer to ensure all women diagnosed with breast cancer have multidisciplinary approaches with early referral to fertility specialists to discuss regarding potential risks and benefits of fertility preservation to improve the uptake of fertility preservation among this group of patients.

Keywords

Fertility Preservation, Ovarian Reserve, Young Women, Early-Stage Breast Cancer

1. Introduction

Breast cancer is the most common cancer in women worldwide with an esti-

mated 2.3 million new cases worldwide in 2020 [1]. Traditionally considered as a disease of post-menopausal women, the incidence among pre-menopausal women is increasing with around 10% of newly diagnosed breast cancer among women less than 40 years old [2]. The management of breast cancer in young women brings unique challenges. Breast cancers arising in young women tend to be of more aggressive subtypes, such as triple negative or HER2 positive, and are more likely to present at an advanced stage, contributing to poorer outcomes [3]. Younger women with breast cancer have a higher rate of germ-line mutations such as BRCA1 and BRCA2 or other genetic mutations, which must be taken into account when considering fertility preservation [4].

Although breast cancer in young women carries a worse outcome overall, the age-standardized mortality rate has decreased from 17 deaths per 100,000 persons in 1968 to 11 deaths per 100,000 persons in 2016 [2]. The decline has been attributed to improvements in treatment and earlier detection. The Australian Cancer Incidence and Mortality Report (2018) reported that the majority of women with breast cancer were diagnosed at an early stage. This was true even for young women aged less than 40 years as 72% were diagnosed with Stage 1 and Stage 2 [2]. Generally, relative survival rates remain high for women with early-stage breast cancer with those diagnosed with Stage 1 exhibiting a survival rate of up to 98% and Stage 2 up to 95% [2].

Studies have shown that at the time of diagnosis, approximately 50% of young women with breast cancer are concerned about becoming infertile [5] and cancer-related infertility is associated with a greater risk of emotional distress and poorer quality of life [6]. Furthermore, a recent meta-analysis has shown that breast cancer survivors who had received adjuvant systemic therapy for breast cancer had only a 14% chance of becoming pregnant and the pregnancy rate is 40% lower than the general population [7]. With the current global trend of delaying childbearing age, there is a growing population of young women who are diagnosed with breast cancer before completing their family [8].

Despite progress in the availability and accessibility of fertility preservation services, the uptake of these services among women undergoing cancer therapy remains poor, with only an estimated 4% - 20% of women undergoing cancer treatment having utilized this service [9]. There are various factors that may contribute to the low uptake of fertility-preserving techniques available for patients with breast cancer, which include urgency to start cancer treatment, inadequate information provided to the patient about treatment-related fertility risk, apprehension about the expected burden of the fertility preserving process itself, the economic impact of fertility treatment on the individual, and disease-related concerns such as fear of future cancer recurrence, treatment-related complications, or fear about the safety of future pregnancies [10].

Current guidelines on fertility preservation in cancer patients highlight the importance of informing all patients diagnosed during their reproductive years about the possible risk of treatment-related Premature Ovarian Failure (POF) and infertility, and of initiating discussion of the different available options for

fertility preservation with patients who are interested in pursuing these services [11]. Oncofertility counselling should be considered as a part of routine clinical practice and should be discussed during the first medical consultation with young patients with newly diagnosed breast cancer.

In this review, we examine the evidence of the impact of treatment for early-stage breast cancer in young patients concerning the consequent loss of fertility which could possibly lead to improved uptake of fertility preservation among this group of patients.

2. Material and Methods

PubMed and Embase databases were searched for studies that included the keywords (breast neoplasm, young women, fertility preservation, ovarian reserved) and MeSH terms (breast neoplasm and young women and fertility preservation). The literature search was restricted to manuscripts published in peer review journals and abstracts in the English language from 2010 to 2021 to evaluate the effect of breast cancer treatment in young women with early-stage breast cancer on their fertility and ovarian reserve.

3. Impacts of Breast Cancer Treatment on Fertility

The risk of infertility related to breast cancer treatment is difficult to assess particularly since the majority of studies have used secondary markers or lack of impact on ovarian reserve, such as return of menses, successful pregnancy and timing of menopause after systemic therapy. The number of patients in the reproductive age group in most studies is small and studies that use more useful markers of ovarian reserve such as serum Anti-Mullerian Hormone (AMH) measurement demonstrate that ovarian reserve may be diminished despite the resumption of regular menses [12]. The algorithm in **Figure 1** summarizes the recommended adjuvant systemic treatment for premenopausal women with early-stage breast cancer focusing on optimal chemotherapy, endocrine therapy and targeted therapy approaches in this specific patient population group [13].

4. Chemotherapy

For triple negative breast cancer, the current standard of care is adjuvant chemotherapy with Anthracycline (AC) and taxane-based (A-T) regimen. Addition of taxane significantly reduces risk of both recurrence and overall mortality (RR: 0.84; 95% CI: 0.78 - 0.91) and (RR: 0.86; 95% CI: 0.79 - 0.93) respectively [14]. For patients in whom anthracycline and taxane is contraindicated, CMF (cyclophosphamide, methotrexate, 5FU) regimen is an acceptable alternative to A-T [15]. Another alternative to reduce side effects of anthracycline is a combination therapy of docetaxel and cyclophosphamide (TC). Meta-analyses of RCTs showed no differences between TC and A-T in Disease Free Survival (DFS) (HR: 1.08; 95% CI: 0.96 - 1.20) and Overall Survival (OS) (HR: 1.05; 95% CI: 0.90 - 1.22); however, a trend favouring A-T was observed in hormone negative and node positive patients [16].

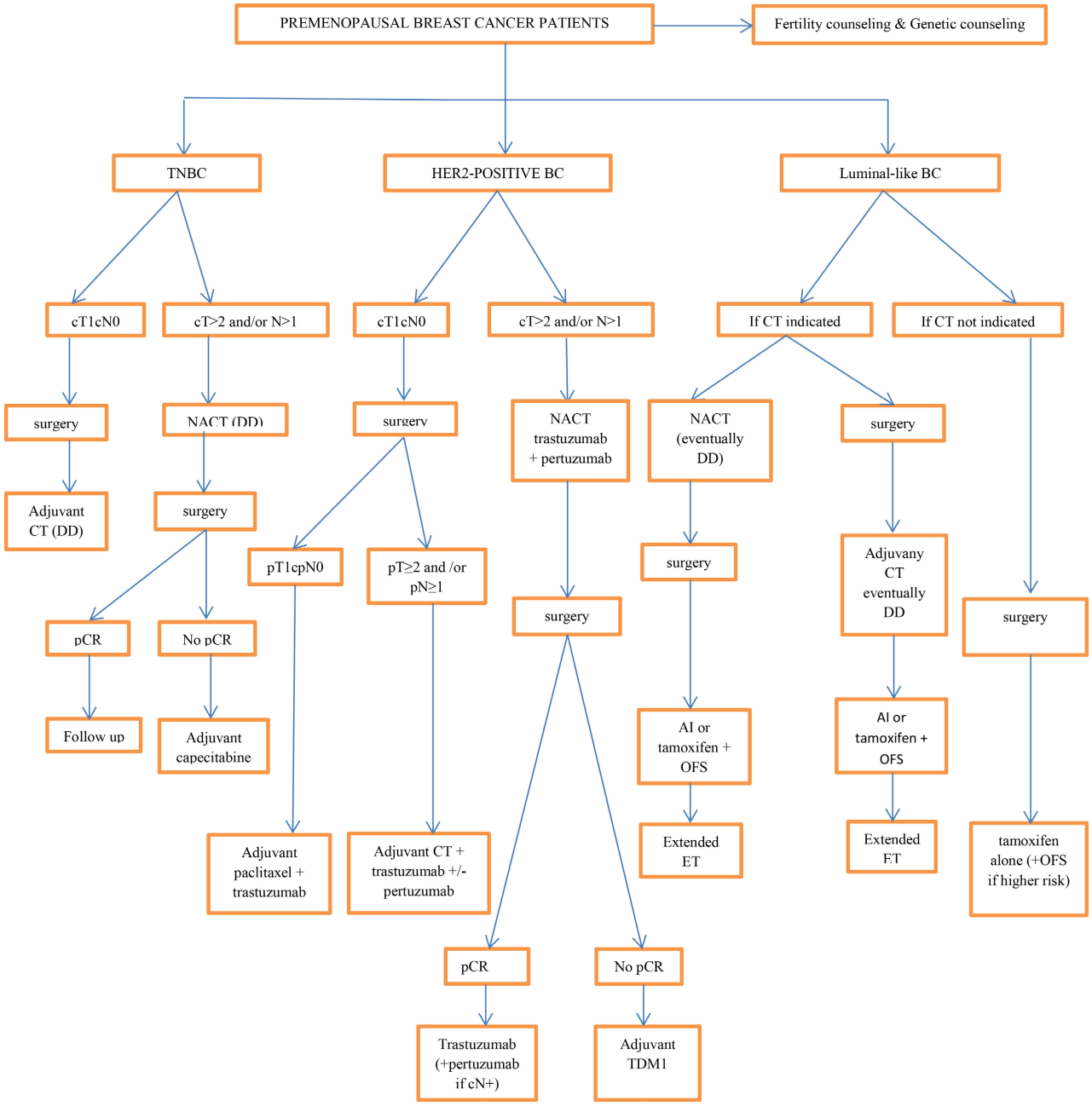

Figure 1. Algorithm for the management of premenopausal patients with early-stage breast cancer. Abbreviations: BC: Breast Cancer; CT: Chemotherapy; DD: Dose-Dense; ET: Endocrine Therapy; HER2: Human Epidermal growth factor Receptor 2; NACT: Neoadjuvant Chemotherapy; OFS: Ovarian Function Suppression; pCR: pathological Complete Response; Tam: Tamoxifen; TDM1: Trastuzumab-emtansine; TNBC; Triple-Negative Breast Cancer. Reprinted with permission from Parisi, F., *et al.* (2020) *Clinical Medicine. Oncology*, **14**, 1-10 [13].

For low risk patient, another alternative to reduce side effects of anthracycline is by administration of weekly paclitaxel and trastuzumab instead of anthracycline and cyclophosphamide in patients with HER2 positive disease. This regimen has lower risk of chemotherapy-induced ovarian failure, however, studies have shown that this regimen only benefited patients with small tumours (<2 cm) and node negative disease only [17].

Recently, the use of neoadjuvant chemotherapy has increased in popularity as achievement of pathological complete response (defined as absence of disease in the breast and nodes during surgery) has a strong prognostic value particularly in HER2 +ve and triple negative disease [18]. For patients who have not achieved a complete pathological response, additional adjuvant chemotherapy with capecitabine has statistically significant improvement in DFS (HR: 0.70; 95% CI: 0.53 - 0.92) and OS HR: 0.59; 95% CI: 0.39 - 0.9) [19].

Another indication for adjuvant chemotherapy is in patients with luminal like disease (ER and PR positive) who have a high risk of recurrence. With the recent development of 21 gene recurrence score assay "Oncotype Dx", we are able to further select the patient who may benefit most from adjuvant chemotherapy. Studies have shown that patients aged less than 50 with recurrence score between 16 and 25 yielded apparent benefits with the use of adjuvant chemotherapy [20].

Generally, almost all chemotherapeutic agents used for breast cancer treatment have a direct impact on fertility because these treatments can lead to either temporary or permanent chemotherapy-related amenorrhea. Cyclophosphamide, an alkylating agent has the highest risk of gonadotoxicity with amenorrhea occurring in 40% - 60% of women younger than 40 years old and in more than 80% in women older than 40 years old, especially when this agent was used in high doses [21]. Anthracyclines are less gonadotoxic than alkylating agents but are still associated with high rates of amenorrhoea.

Parulekar *et al.* (2005) compared the incidence of amenorrhea in patients treated with anthracycline (CEF) versus cyclophosphamide (CMF) and found that despite a higher cumulative dose of cyclophosphamide in the CMF group at 6 months post randomization, the rate of amenorrhea was higher in the CEF group (RR: 1.2; 95% CI: 1.0 - 1.3). Despite this, there was no difference in rate of amenorrhea in both groups at 12 months post randomization [22].

A recent meta-analyses by Zavos *et al.* (2016) on risk of Chemotherapy Induced Amenorrhoea (CIA) in patients with breast cancer found that CIA was increased by age with an estimate of 26% (95% CI: 12 - 43), 39% (95% CI: 31 - 58) and 77% (95% CI: 71 - 83) for women < 35 years, 35 - 40 years and >40 years old respectively. When looking the risk for CIA according to adjuvant chemotherapy regimen and age, they showed that women > 40 years old treated with either CMF or anthracycline-base chemotherapy other than ACx4 had the highest risk for CIA (>70%). The low-risk group for CIA (<30%) included women < 35 years old irrespective of chemotherapy, as well as women <40 years old that were treated with either anthracycline or taxane based chemotherapy or with ACx4 [23].

As for low risk patients who received paclitaxel and trastuzumab therapy, study of APT trials showed that the rate of long term amenorrhea was 28% (95% CI: 18% - 41%; median 4 years after chemotherapy initiation) in patients who received paclitaxel and trastuzumab therapy [24].

When we assessing AMH level, almost all showing marked decline in AMH

value after chemotherapy. Study by Freour *et al.* (2017) evaluating the evolution of AMH in women with breast cancer treated with chemotherapy found that generally AMH levels rapidly fall to undetectable levels in most women during chemotherapy and persist at a very low level after treatment [25].

A recent meta-analysis by Romito A. *et al.* (2021) evaluated the effect of chemotherapy on AMH value also demonstrated a marked decline of AMH value after chemotherapy. Although a few months later there was a slight recovery, AMH value remained in the poor responder's threshold. Another interesting finding from this analysis was AMH value appear to be very low for women older than 35 years of age (mean AMH values one year after chemotherapy for the age category were 0.24 ± 0.69, 0.15 ± 0.77 and 1.14 ± 1.65 ng/mL for >40 years old, 35 - 40 years old and 30 - 35 years old subgroup respectively. Therefore for these patients pre treatment counselling should be mandatory to inform them about the expected fertility drop and fertility preservation might be implemented before hand in women who desire fertility treatment [26].

Lambertini *et al.* (2019) has studied the effect of taxane in young women with early breast cancer who received either 6 cycles of FEC (5FU 500 mg/m^2, epirubicin 100 mg/m^2, cyclophosphamide 500 mg/m^2) or 3 cycles FEC followed by 3 cycle of docetaxel (D, 100 mg/m^2). In the whole cohort, AMH level drastically dropped 1 year after diagnosis ($p < 0.0001$) and at 3 years there were no differences in AMH level between the two groups [27].

From the available evidence, almost all chemotherapeutic agents will have some impact on ovarian reserve; this is especially well demonstrated in the studies which observed more conclusive markers such as AMH.

5. Targeted Therapy

In patients with HER2 positive breast cancer, the advent of adjuvant trastuzumab has improved prognosis. The addition of trastuzumab to standard chemotherapy reduces the risk of recurrence by approximately 40% and the risk for death up to 34%. The benefits of trastuzumab are independent of age, tumour size, lymph node status, or Hormone Receptor (HR) status. Therefore, chemotherapy plus trastuzumab-based treatment for 1 year is the current standard of care for most patients with HER2 positive disease [17]. In the era of dual anti HER2 therapy, addition of pertuzumab to trastuzumab will result in greater rates of a pathologically complete response following neoadjuvant chemotherapy, as well as a reduction in disease recurrence. A study by Chiu *et al.* in 2019 identified that the addition of trastuzumab to chemotherapy regimens have improved the pathological complete response from 5% to 26% and the addition of a second anti HER2 therapy pushed the rate to 62% [28].

The available data suggests no significant additive impact on amenorrhea following 1 year of trastuzumab therapy. A recent study by Lambertini *et al.* (2019) on the impact of adjuvant anti HER2 therapy on CIA following completion of chemotherapy reported no significant difference in the incidence of CIA in all

four groups. The CIA rates were 72.6%, 74.0%, 72.1% and 74.8% in the trastuzumab, lapatinib, trastuzumab followed by lapatinib and trastuzumab and lapatinib arms, respectively (p = 0.64). When compared to trastuzumab alone, no difference in CIA risk was observe with lapatinib (OR: 1.13; 95% CI: 0.9 - 1.43; p = 0.29), trastuzumab followed by lapatinib (OR: 0.99; CI: 0.79 - 1.24; p = 0.91) and trastuzumab and lapatinib (OR: 1.19; 95% CI: 0.94 - 1.51; p = 0.14) [29]. The only factors that remained statistically significant when assessing CIA were older age at diagnosis, addition of taxane and use of adjuvant endocrine therapy. The absence of higher CIA rate in the dual blockade arm, as compared to single arm, may suggest the gonadal safety with these agents [29].

Although, treatment with anti HER2 therapy may not contribute to amenorrhea, systematic review and meta-analyses by Zagouri *et al.* (2013) recommended that any attempts for pregnancy should be delayed for at least 7 months after completion of anti HER2 therapy due to risk of teratogenicity [30].

6. Endocrine Therapy

Tamoxifen has been the standard of care for many years as adjuvant endocrine therapy for premenopausal women with hormone receptor positive breast cancer [31]. Despite 5 years of adjuvant endocrine therapy, hormone receptor positive tumours retain a substantial risk of late recurrence. Prognostic factors for late recurrence include anatomic stage (tumour size and nodal status), high grade tumour and high risk score on genomic assay. ASCO clinical practise guideline focused update (2018) has recommended for women diagnosed with hormone receptor positive breast cancer who are pre-menopausal should be offered tamoxifen for 5 years. After 5 years, patients with higher risk of recurrence should continue with extended endocrine therapy based on menopausal status. If they are premenopausal or of unknown status, they should continue tamoxifen for another 5 years [31]. If they have undergone menopause, they may continue tamoxifen or switch to an Aromatase Inhibitor (AI) for another 5 years. Studies have shown that extended endocrine treatment for 10 years has significant improvement in DFS (HR: 0.26; 95% CI: 0.13 - 0.55) and better OS (HR: 0.43; 95% CI: 0.08 - 2.22) [32].

More recently several studies have reported on the role of Ovarian Function Suppression (OFS) in addition to tamoxifen or to an Aromatase Inhibitor (AI). The higher the risk of recurrence, the larger the expected benefit and thus the preference for the combination of OFS and an AI [33]. ASCO 2018 has recommended ovarian suppression in addition to standard endocrine therapy only for high-risk pre-menopausal women [31].

Several studies have shown an increase risk of post-treatment amenorrhea when tamoxifen was administered after chemotherapy. Rather than representing a true gonadotoxic effect of tamoxifen, this likely reflects the known association of tamoxifen with menstrual irregularities [34]. Study on endocrine therapy gonadotoxicity measured by AMH levels did not show any difference between pa-

tients who received tamoxifen and those who did not undergo chemotherapy. There are also interesting findings of a higher level of AMH at one year in women who used tamoxifen compared to women who received chemotherapy alone [27].

Women on endocrine therapy have an overall reduced rate of post treatment pregnancies compared to women who are not on endocrine therapy [34]. Another study also reported fertility concerns negatively impacted tamoxifen initiation and continuation among premenopausal women with breast cancer [35]. An international study is currently ongoing to investigate the safety of a temporary interruption of endocrine therapy after 18 to 30 months of treatment to allow a pregnancy (POSITIVE trial) [36].

7. Safety of Pregnancy after Breast Cancer

Many patients and physicians remain concerned about the potential detrimental effects of pregnancy after breast cancer in term of reproductive outcomes and maternal safety. There are a few meta-analyses focus on this subject and its shows pregnancy in breast cancer survivors does not have a negative prognostic impact, regardless of the hormone receptor status of the tumour. Recent meta analysis by Lambertini *et al.* (2021) involving 112,840 patients with breast cancer of whom 7505 had a pregnancy after diagnosis showed the chance of pregnancy was significantly lower compared to general population (RR: 0.4; 95% CI: 0.32 - 0.49). Risk of caesarean section (OR: 1.14; 95% CI: 1.04 - 1.25), low birth weight (OR: 1.50; 95% CI: 1.31 - 1.73), preterm birth (OR: 1.45; 95% CI: 1.11 - 1.88) and small for gestational age (OR: 1.16; 95% CI: 1.01 - 1.33) were significantly higher in breast cancer survivors particularly in those with previous chemotherapy exposure, compared to general population. No significantly increase risk of congenital abnormalities or other reproductive complications were observed. Compared to patients with breast cancer without subsequent pregnancy, those with pregnancy had better disease free survival (HR: 0.66; 95% CI: 0.49 - 0.89) and overall survival (HR: 0.56; 95% CI: 0.45 - 0.68). Similar results were observed after correcting for potential confounders and irrespective of patient, tumour and treatment characteristics, pregnancy outcome and timing of pregnancy [37].

These studies provide reassuring evidence on the long-term safety of pregnancy in breast cancer survivors including those with HR positive disease. Hence, after completed breast cancer treatment and follow up, pregnancy in breast cancer survivors should not be discouraged.

8. Safety and Efficacy of Controlled Ovarian Hyperstimulation (COH)

Breast cancer could theoretically be stimulated by the temporarily hyperestrogenic state during the controlled ovarian hyperstimulation procedure. To reduce the possible deleterious hyperestrogenic effect, letrozole or tamoxifen are recommended during ovarian hyperstimulation in patients with a recent breast cancer diagnosis [38]. A systematic review uniformly demonstrated that the admini-

stration of letrozole during COH reduced oestrogen levels without substantially reducing oocyte yield [39]. So far, there is no evidence to suggest a higher recurrence rate of breast cancer in woman who opt for a fertility preservation procedure after breast cancer diagnosis, although the follow up period of most studies are short [40].

Another strategy to increase the safety of COH is to add a GnRH agonist trigger. It is purported to produce a faster decline in oestradiol concentrations following oocyte collection, and thus reduce the risk of ovarian hyperstimulation. GnRH agonists also give the advantage of a greater mature oocyte yield without an associated reduction in pregnancy or live birth rates in cryopreservation cycles [41].

9. Fertility Preservation Treatment

Embryo cryopreservation is an established fertility preservation method and is available worldwide, and has routinely been used for storing surplus embryos after *in vitro* fertilization. Despite its popularity, there still remains an ethical concern on the outcome of the embryo should there be a relationship or patient demise following oncology treatment.

In light of this, there has been a recent surge in the cryopreservation of unfertilized oocytes. This modality may be especially well-suited to women who do not have a male partner, do not wish to use donor sperm, or have religious or ethical objections to embryo freezing. With the improvement in cryopreservation techniques, frozen oocyte currently is considered equivalent to fresh oocyte with a recent study showing that up to 85% of oocytes will survive the freeze and thaw process. This study also reported that live birth rates and perinatal outcomes are similar between transferred frozen embryos (35%) and transferred frozen oocyte-derived embryos (39%) [42].

The procedure for oocyte retrieval for embryo cryopreservation or oocyte cryopreservation is considered minimally invasive, and a treatment cycle can be completed in two to three weeks, avoiding any delay in intended cancer treatment. In a patient who requires urgent treatment, random start can be offered. Random start ovarian stimulation can shorten the interval between ovarian stimulation and oocyte retrieval with the yield of oocytes and embryos being comparable to conventional stimulation protocol [43].

In contrast to embryo or oocyte cryopreservation, Ovarian Tissue Cryopreservation (OTC) and transplantation are still considered experimental. Recently, the American Society for Reproductive Medicine has removed OTC from its list of experimental procedures in 2019. Ovarian tissue cryopreservation involves surgical excision of ovarian tissue followed by cryopreservation of carefully prepared strips of ovarian tissue. When childbearing is desired, autologous transplantation of the cryopreserved ovarian tissue can be performed. A recent meta-analysis examining studies of ovarian tissue transplantation found a cumulative clinical birth rate of 57.5% [44]. Current concerns include potential reseed-

ing of malignant cells with autologous ovarian tissue transplantation. Although the risk of reintroducing malignant cells cannot be completely eliminated, case series have not, to date, identified this as a clinically significant problem provided that testing for presence of malignant cells was performed at the time of tissue cryopreservation [45].

As for ovarian suppression, there is conflicting evidence as to the suitability of the use of GnRH agonists and other means of ovarian suppression for fertility preservation. ASCO has recommended that in the setting of young women with breast cancer where standard fertility preservation methods such as oocyte, embryo, or ovarian tissue cryopreservation are not feasible, GnRH agonists may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency. However, GnRH agonists should not be used in place of proven fertility preservation methods [31].

10. Conclusion

Treatment for young women with breast cancer often will result in either depletion of ovarian reserve or age-related infertility. The age of the patient, the type, and the dose of chemotherapy are the main factors determining the magnitude of the damage in the ovary. Fertility preservation should be discussed with all women of reproductive age with breast cancer, particularly in the subset of the population that is at greatest risk of significant loss of fertility, or those who are at risk of significant emotional burden due to the loss of fertility. Women should be counseled on whether to store gametes or embryos before treatment, which includes a transparent prognosis of the likelihood of losing fertility as a result of cancer treatment.

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Conflicts of Interest

The authors declare no conflict of interest.

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