PROVISION OF FERTILITY PRESERVATION FOR YOUNG WOMEN WITH EARLY-STAGE BREAST CANCER

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BACKGROUND

Standard treatment for breast cancer can impair fertility. Fertility preservation before cancer therapy may offer the best opportunity to allow a patient to have a family later in life.

INTRODUCTION

Breast cancer is the most common cancer in women worldwide, constituting 25% of all cancer diagnoses (1). In 2018 alone there were an estimated 2.1 million new cases of breast cancer, indicating a 20% increase from 2008 (2). 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).

Approximately 50% of young women with breast cancer are concerned about becoming infertile, (4) and cancer related infertility is associated with a greater risk of emotional distress and poorer quality of life (5).

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, with the pregnancy rate 40% lower than the general population. (6)

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, however only an estimated 4-20% of women undergoing cancer treatment having utilized this service.(7)

Oncofertility counselling should be considered as part of routine clinical practice and should be discussed during the first medical consultation with young patients with newly diagnosed breast cancer.

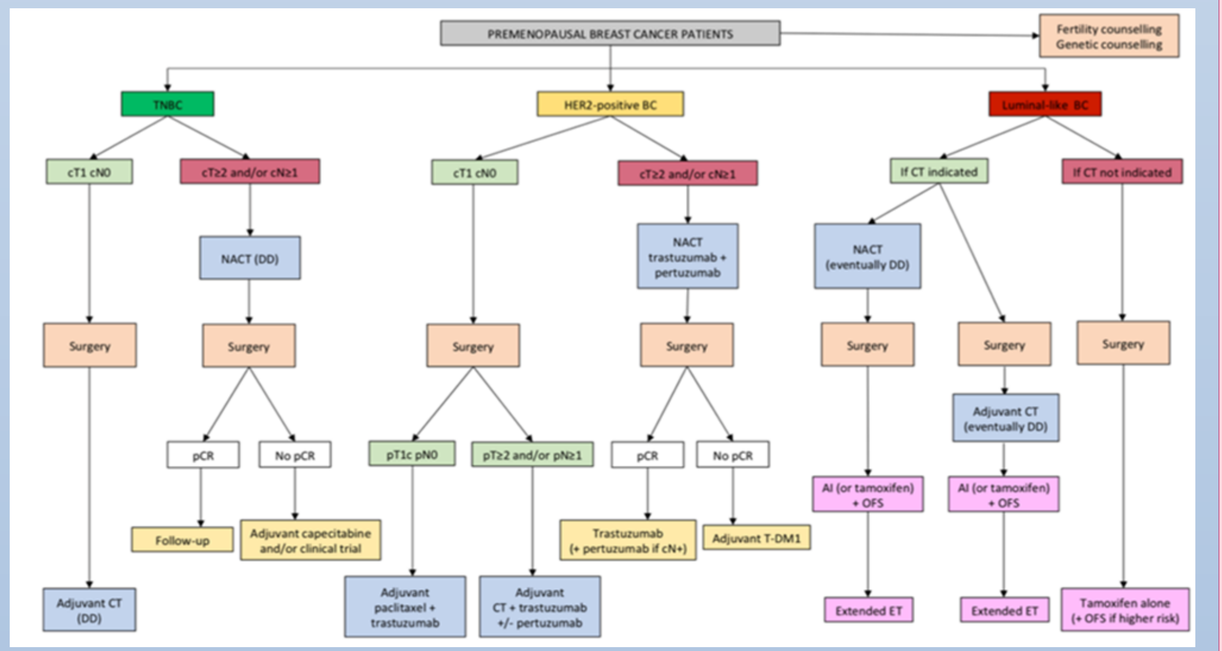

Figure 1. Algorithm for the management of premenopausal patients with early breast cancer.
Abbreviations: BC, breast cancer; CT, chemotherapy; DD, dose-dense; ET, endocrine therapy; HER2, Human Epidermal growth factor Receptor 2; NACT, neoadjuvant chemotherapy; OFS, ovarian function suppression; pCR, pathological complete response; Tam, tamoxifen; TDM1, trastuzumab-emtansine; TNBC, triple-negative breast cancer.

METHODS

A systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline for the years 2010-2020 inclusive and included the search terms ‘breast neoplasm’ (MeSH) AND ‘young women’(MeSH) AND ‘fertility preservation’ (MeSH). The EMBASE search strategy consisted of the terms: ‘Breast Cancer’ AND ‘Ovarian Reserve’ OR ‘Fertility Preservation’ OR ‘Pregnancy’ OR ‘Ovarian Failure’. 424 articles were initially screened with 153 articles included for full text review including 2 clinical guidelines.

RESULTS

The majority of the studies used resumption of menses as an indirect measurement of ovarian reserve and thus fertility.

The rate of chemotherapy induced amenorrhea (CIA) increased by age, with an estimate of 26%, 39% and 77% for women <35 years old, 35-40 years old and >40 years old, respectively

Current standard chemotherapy regimens which are 3rd generation anthracycline based [ACx4 (anthracycline/cyclophosphamide) and anthracycline- taxane-based (anthracycline,cyclophosphamide followed by taxane)] have shown to have lower risk of CIA compared to traditional CMF (cyclophosphamide, methotrexate, 5FU) and anthracycline based (CEF/CAF i.e. cyclophosphamide, epirubicin/adriamycin, 5FU).

DISCUSSION

Chemotherapy

For triple negative breast cancer, the current standard of care is adjuvant chemotherapy with anthracycline (AC) and taxane-based (A-T) regimem.

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 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 cyclophophamide was used in high doses (8). A 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 (9). 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.

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.

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. 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 (10,11,12). Women on endocrine therapy have an overall reduced rate of post treatment pregnancies compared to women who are not on endocrine therapy (13).

Safety of Pregnancy After Breast Cancer

Pregnancy in breast cancer survivors does not have a negative prognostic impact, regardless of the hormone receptor status of the tumour. In the meta-analysis by Azim *et al.,* (2011), which included 14 retrospective control-matched studies with 1,244 cases and 18,145 controls, breast cancer survivors who were pregnant at follow-up showed a 41% reduced risk of death compared to patients who did not become pregnant (pooled relative risk [PRR]: 0.59; 95% CI: 0.50-0.70)(14). Another study assessing the prognosis of women diagnosed with breast cancer before, during and after pregnancy found that pregnancy that occurs before or concurrently with a diagnosis of breast cancer is more likely to result in death and decreased DFS. On the other hand, pregnancy following breast cancer diagnosis had a significantly reduced risk of death compared to those who did not become pregnant (HR:0.63; 95% CI:0.51-0.79) (15).

CONCLUSION

Treatment for young women with breast cancer often will result in either depletion ovarian reserve or age-related infertility. The age of the patient, the type and 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.

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