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Review

Strategies for fertility preservation in young early breast cancer patients

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ABSTRACT

Diagnosis of breast cancer in young women poses a threat to fertility. Due to a recent trend of delaying pregnancy, an increasing number of breast cancer patients in reproductive age wish to bear children. Health care providers have the responsibility to know how to manage fertility issues in cancer survivors. Oncofertility counseling is of great importance to many young women diagnosed with cancer and should be managed in a multi-disciplinary background. Most of young breast cancer patients are candidate to receive chemotherapy, which could lead to premature ovarian failure. A baseline evaluation of ovarian reserve may help in considering the different fertility preservation options. The choice of the suitable strategy depends also on age, type of chemotherapy, partner status and patients' motivation. Various options are available, some established such as embryo and oocyte cryopreservation, some still experimental such as ovarian tissue cryopreservation and ovarian suppression with GnRHa during chemotherapy. An early referral to a reproductive specialist should be offered to patients at risk of infertility who are interested in fertility preservation.

Introduction

About 12% of breast cancers are diagnosed in women younger than 44 years of age [1]. Tumors that occur in young women seem to be more aggressive than the one arising in older patients [2], with higher rate of nodal disease, triple negative immunohistochemical profile and need of systemic treatments [3,4]. Adjuvant chemotherapy and endocrine treatments have improved both disease-free survival (DFS) and overall survival (OS) in young breast cancer patients [5], but may cause acute and chronic side effects, including ovarian function loss. Chemotherapy related-infertility and early menopause cause psychological distress and negative impacts on global health of young breast cancer survivors [6]. Moreover, due to the fact that women decide to have children at a later stage of life, they can be childless or may want to enlarge their family at the time of breast cancer diagnosis [7].

Health care providers should be knowledgeable about guidelines on fertility preservation in cancer patients [8–10]. They have the responsibility to raise awareness on potential fertility problems related to cancer and anticancer treatments and should be able to deal with these issues. Every young patient who is candidate to chemotherapy should receive information about ovarian damage due to cancer treatments. In fact, irrespective of the occurrence of transient amenorrhea following anticancer therapies, young cancer patients are at risk of losing fertility nonetheless, due to a depletion of the ovarian reserve [11,12]. If patients show interest about future procreation, physicians should reassure them that pregnancy after breast cancer is possible, and that a previous diagnosis of breast cancer does not increase the obstetrical or oncological risk. Fertility preservation options should be illustrated, highlighting success rates, costs, as well as the risks inherent to the procedures and their ethical implications [13].

The purpose of this paper is to review the literature on fertility issues in young breast cancer patients and to focus on the key points of appropriate counseling, including evaluation of ovarian reserve, discussion about chemotherapy-induced gonadotoxicity and the impact of a subsequent pregnancy on breast cancer

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prognosis, as well as a description of all the available options to preserve fertility.

Ovarian reserve and prediction of ovarian damage due to anticancer treatments

The ovaries have a reserve of primordial follicles, progressively depleting during reproductive life [14]. These follicles cannot regenerate. Some antineoplastic agents increase the rate of follicle loss, inducing premature ovarian failure (POF). POF leads to infertility and early menopause, and is associated with hot flashes, sexual dysfunction, mood disturbances and an increased risk of osteoporosis.

The assessment of ovarian reserve is best performed through antral follicle count, follicle-stimulating hormone (FSH), estradiol and anti-Mullerian hormone (AMH) [15,16]. Among these, AMH levels seem to be the most reliable and promising marker of remaining fertility after chemotherapy [17]. AMH is produced by the granulosa cells of small antral follicles: its levels are proportional to primordial follicle count and seem a good estimate of ovarian reserve. They are also used to predict ovarian response to a hormonal stimulation and *in vitro* fertilization (IVF) treatment [18]. Nevertheless, future researches are needed to better define the clinical role of AMH in patients with early breast cancer, particularly its role in predicting treatment-induced infertility.

Ovarian reserve should guide fertility counseling, as it may influence the impact of chemotherapy on further reproduction and the success of fertility preservation techniques [13]. Amenorrhea is often used as a synonym of ovarian damage, but it is a rather inaccurate marker of fertility. Women may have regular menses after chemotherapy but may be subfertile, and vice versa.

Unfortunately, data on molecular markers of ovarian damage are limited and further studies are needed in order to investigate their role as predictors of chemotherapy-induced gonadotoxicity.

Chemotherapy-induced gonadotoxicity

Antineoplastic drugs are known to have different gonadotoxicity. The rate of chemotherapy related infertility is variable and depends on several factors: class, dose, dose-intensity of the drug used, method of administration (oral vs intravenous), age of the patient, disease, history of previous treatment for infertility and comorbidities (Table 1) [8].

High risk of ovarian failure is associated with alkylating agents like cyclophosphamide. Anthracyclines alone and anthracyclines in association with taxanes have an intermediate risk, whereas methotrexate and 5-fluorouracil demonstrate low risk of ovarian damage [19,20].

Chemotherapy-induced ovarian toxicity has been attributed to two major mechanisms: direct induction of oocyte apoptosis and indirect effect via stromal damage.

Morphological observations demonstrate a reduction in primordial follicle stockpiles and vascular damage with infarcts related to hyalinization of ovarian cortical vessels, intimal fibrosis and thickening of the muscular layer [21,22]. Furthermore, subcapsular cortical fibrosis has also been described with reduced ovarian weight and macroscopic signs of atrophy after chemotherapy [22].

A recent *in vivo* study analyzed the effect of cyclophosphamide administration on the ovaries of mice [23]. Physiologically dormant primordial follicles represent the ovarian reserve: once activated, they initiate unidirectional and irreversible growth until ovulation or atresia. In normal ovaries there is a balance between activation and inhibition factors that maintain most of the primordial follicles in a dormant state. It was observed that cyclophosphamide disturbs this equilibrium, inducing an increase in follicle activation. Hence, growing and proliferating follicles become susceptible to cyclophosphamide-induced apoptosis. Continuous recruitment of primordial follicles into activation, growth and apoptosis cause ovarian reservoir burnout [23].

Table 1
Risk of permanent amenorrhea in breast cancer patients treated with anticancer therapies [modified from the original [8]].

Degree of risk	Type of anticancer treatment
High risk (>80%)	- CMF, CEF, CAF, TAC × 6 cycles in women ≥40 years.
Intermediate risk	- CMF, CEF, CAF, TAC × 6 cycles in women age 30–39; -AC × 4 cycles in women ≥40 years; - AC or EC × 4 → T.
Lower risk (<20%)	- CMF, CEF, CAF, TAC × 6 cycles in women ≤30 years; - AC × 4 cycles in women ≤40 years.
Very low or no risk	- Methotreaxte; - Fluorouracil; - Tamoxifen; - GnRHa in women ≥40 years;
Unknown risk	- Monoclonal antibodies (trastuzumab).

Abbreviations: CMF, cyclophosphamide/methotrexate/fluorouracil; CEF, cyclophosphamide/epirubicin/fluorouracil; CAF, cyclophosphamide/doxorubicin/fluorouracil; TAC, docetaxel/doxorubicin/cyclophosphamide; AC, doxorubicin/cyclophosphamide; EC, epirubicin/cyclophosphamide; T, taxane; GnRHa, gonadotropin releasing hormone analogues.

Influence of pregnancy on breast cancer prognosis

Historically, based on purely theoretical assumptions, pregnancy after breast cancer was not recommended due to the fear of a potential negative impact on patients' prognosis. Recent clinical data do not confirm such hypothesis and all the available evidences suggest that spontaneous pregnancy after breast cancer does not affect prognosis.

Case–control and population-based studies have been conducted to evaluate survival in women who become pregnant after breast cancer. The hormonal changes during pregnancy are complex and do not seem to have a negative impact on breast cancer prognosis [24].

A meta-analysis of fourteen studies reported a significant improvement in OS with a 41% reduced risk of death (pooled relative risk [PRR]: 0.59; Confidence Interval [CI]: 0.50–0.70) in women who became pregnant after breast cancer compared with those who did not get pregnant after cancer [25]. Some authors introduced the concept of the "healthy mother effect" [26]: a possible explanation of this improved outcome could be the selection bias of healthier women. To investigate this confounding factor, a subgroup analysis was performed in the previously cited meta-analysis, restricting the field to non-relapsing patients. Pregnant women maintained a non-statistically significant trend toward better survival [25].

Recently, a multicenter retrospective cohort study with the aim to better clarify the impact of pregnancy on DFS in breast cancer patients according to estrogen receptor status was published [27]. No difference in DFS was observed between pregnant and non-pregnant patients in the estrogen-receptor-positive group (the primary end point of the study: hazard ratio [HR]: 0.91; 95% CI: 0.67–1.24) or in the estrogen receptor negative cohort (HR: 0.75; 95% CI: 0.51–1.08). However the pregnant group showed a better OS with a 28% reduced risk of death (HR: 0.72; 95% CI: 0.54–0.97) without an interaction with the estrogen receptor status [27].

Hence, it is reasonable to state that pregnancy after breast cancer could be considered safe even for patients with a history of endocrine-sensitive breast cancer, and that women should not be discouraged in completing their family plan.