

Breast cancer: Treatment effects on fertility and subsequent pregnancy outcomes

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ABSTRACT

Objective: Breast cancer is the most common cancer type in women of reproductive age. Given that most women postpone childbearing, breast cancer occurrence possibly perplexes their plans for starting a family. The treatment for breast cancer can affect their fertility and have adverse effects on a pregnancy that occurs during that period. The aim of this narrative review is primarily to explore the influence of breast cancer therapy on the ability of a woman diagnosed with breast cancer to gestate. Moreover, to determine the safer timing for childbearing after being treated for breast cancer and investigate the pregnancy outcome when conception is succeeded.

Childbearing after treatment for breast cancer is considered safe and pregnancy outcomes are favorable if conception happens one year after chemotherapy or at least two years after chemotherapy and radiation therapy. Counseling is of great significance, and fertility preservation methods should be thoroughly discussed with women diagnosed with breast cancer, even prior to commencement of the treatment.

Keywords: breast cancer, fertility, pregnancy, treatment, review

INTRODUCTION

Breast cancer is the most common type of cancer in women of reproductive age, as about 10% of the cases are diagnosed before the age of 40, with the mean age of diagnosis being 33 years (range 23-47) (1). However, 60% of the cases can be successfully treated with early diagnosis, surgery, and adjuvant systematic therapy (2).

The breast is an organ with great plasticity which undertakes numerous and complex developmental changes throughout a woman's life, capable of permanently altering the mammary gland by promoting oncogenesis or preventing it. Breast oncogenesis mimics mechanisms happening most commonly during gestation, such as "augmented cell proliferation, decreased cell apoptosis, altered gene expression and extracellular matrix modifications" (3)

Breast Cancer and fertility

As noted previously, most women diagnosed with breast cancer are of reproductive age. The therapies usually used for breast cancer treatment have an impact on women's ability or even the circumstances to become pregnant. Factors such as ovarian insufficiency, delay of childbearing due to therapy administration, inability to breastfeed, even future fertility concerns constitute major hindrances for those women (4).

The fact that contemporary women delay childbearing enhances the importance of matters such as fertility preservation after breast cancer diagnosis and subsequent pregnancy (5). In the paragraphs below the effect that substances used for breast cancer treatment have on fertility is described. Once breast cancer is diagnosed, a multidisciplinary approach should be taken. This includes obstetricians, surgeons, medical and radiation oncologists, and breast cancer counsellors (6).

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Even though radiation scatter to the uterus and ovaries while treating breast/axillary cancer should be minimal, it is recommended that the pelvic area be shielded during the procedure and becoming pregnant should be delayed until after the completion of radiation therapy (4). Furthermore, any fertility treatment (e.g. collecting or fertilizing eggs for future use) should commence before radiation treatment in case the tiny amounts of radiation that reach the eggs that begin maturing affect them. Nonetheless, this amount of radiation is not likely to affect immature eggs inside the ovaries (7).

Chemotherapy

With young age being a poor prognostic factor, women of this age group are often advised (neo)adjuvant chemotherapy (8). One of the more frequent side effects of chemotherapy in women of reproductive age is changes in the menstrual period -such as premature menopause and impaired fertility- which may arise or be permanent. Not all chemo-drugs have the same likelihood to provoke those side effects (9).

American Cancer Society (9) advises women who undertake chemotherapy treatment and want to become pregnant, to refer to their doctor about this matter before starting the treatment.

Endocrine Therapy

Even though pre-menopausal women are most likely to be diagnosed with hormone receptor-negative breast cancer, two-thirds of them will still have estrogen receptor-positive breast tumors (5). In these cases, adjuvant endocrine therapy should be considered (10).

Tamoxifen or aromatase inhibitors therapy has been proven beneficial as adjuvant anti-hormonal therapy for premenopausal women with hormone receptor-positive breast cancer. This type of cancer is characterized by the long-term risk of recurrence and for that reason, 10-year duration of tamoxifen treatment is recommended for many patients (8). Such a long treatment period could lead to natural ovarian reserve decline as a result of the woman's age (10). What's more, tamoxifen's teratogenic effect being well-known, concerns have been risen with regard to fertility and pregnancy and so, tamoxifen treatment is often discontinued or not initiated at all (4).

The ovarian function should be monitored when tamoxifen is used after chemotherapy, in case of unnoticed ovarian function recovery, to avoid teratogenesis or unplanned pregnancies (8).

Fertility preservation

Cancer survivors' fecundity levels are lower than the general population's. As precedently mentioned, chemotherapy is usually suggested as part of treatment for breast cancer to women of younger age, which can lead to premature ovarian insufficiency and cause impaired fertility, a fact that may affect the therapy plan of choice (10). Currently, there are options to consider for preserving fecundity, hence detailed counseling is of grave importance so women diagnosed with breast cancer can make the most optimal decision for them (8).

According to the European Society of Clinical Oncology (ESCO) (11), the recommended solutions for the preservation of fertility are embryo/oocyte cryopreservation for future use. In the case of breast cancer, GnRHa administration is a feasible choice in order to avoid chemotherapy-induced ovarian insufficiency. Ovarian tissue cryopreservation for future transplantation can be chosen to be performed immediately and without ovarian stimulation.

Prevention of ovarian deficiency could be preferred on fertility preservation grounds over freezing oocytes, embryos or ovarian tissue. Despite the usage of Gonadotropin-Releasing Hormone Analogues has been presumed as an agent for protecting the gonads, the mechanism resulting in the gonad protection is not fully understood (8).

Pregnancy after breast cancer treatment

Women longing for a child after the diagnosis of breast cancer, have two main concerns: the impact of treatment on fertility and a subsequent negative consequence of the pregnancy on prognosis. Women with breast cancer history have the lowest pregnancy rate among other types of cancers, namely a 67% reduction chance for pregnancy due to gonadotoxic treatments provoking ovarian reserve damage, but also due to patient and provider concerns about a pregnancy affecting negatively the evolution of breast cancer, the latter being a hormonally driven disease. Withal, according to available evidence, the prognosis of a woman treated for breast cancer won't be negatively impacted by becoming pregnant and so childbearing should be considered safe and should not be discouraged (10).

Knowing about the effects of chemotherapy and antihormonal therapy on fertility, proper information of patients should be mandatory. Up to 40% of women receiving chemotherapy for breast cancer experience a chemotherapy-induced amenorrhea (CIA) (12). Incidence depends on age and treatment regimen. In general, younger patients are less likely to suffer from CIA. A treatment by CMF (cyclophosphamide, methotrexate, 5-fluoruracil) seems to induce more amenorrhea than a regimen with ACT (doxorubicin, cyclophosphamid, paclitaxel) or AC (doxorubicin, cyclophosphamid). It has also been shown that the anti-Müllerian hormone level decreases significantly during chemotherapy (13). Nevertheless, it is actually impossible to predict individual fertility after chemotherapy. For this reason, all women who did not complete child bearing at diagnosis, should be informed about the different possibilities of fertility preservation including GnRH analogues, cryoconservation of oocytes or ovarian cortex. For the choice of the method for fertility preservation the individual prognosis, impact of therapy on ovarian function and delay of treatment should be considered. The appropriate interval between cancer and pregnancy remains unclear. The main concerns are the fear of recurrence and the interruption of antihormonal treatment. Patients should be counselled individually regarding tumor biology and prognosis. In patients with hormone-receptor negative breast cancer a delay of 2–3 years according to prognosis should be respected. Despite the contemporary data and knowledge, the time period demanded between the completion of therapy and conception is not totally clear. Experts suggest the timing should be decided considering the age of the patient and her ovarian reserve, the time of completion of previous therapies and the individual risk for relapse (10).

Concerning chemotherapy, the recommendation is that women postpone pregnancy for 6 to 12 months after chemotherapy treatment, so they do not conceive with an oocyte that was maturing during treatment. Hartnet et al. (14) refer to chemotherapy being known to kill rapidly dividing cells so, "it might damage the oocytes being recruited for ovulation, resulting in higher risks of miscarriage and birth defects in pregnancies conceived soon after treatment" (14).

When using anti-HER2 therapy (e.g. trastuzumab and pertuzumab) it is recommended that childbearing should be delayed for at least 7 months after completion of the therapy, due to its teratogenic effect (4).

Tamoxifen's effects on the fetus and gestation are adverse and the epithelial changes observed resemble those of diethylstilbestrol (DES) (2) so it is recommended that women who undergo tamoxifen treatment use non-hormonal barrier contraception which should continue up to 3 months afterwards (15).

Pregnancy outcome

Pregnancy outcome, pertaining to the neonatal well-being, is not different from the neonatal outcome of the general population. However, the rates of induced abortion observed succeeding breast cancer diagnosis, reach 30% and the incidence of birth complications -such as caesarean section, preterm birth, low birth weight neonates- is higher in breast cancer survivors than in general population. Overall, pregnancy in such cases should be closely monitored (10).

Findings of population-based studies indicate that the birth outcome of women who have breast cancer history may correlate with 50% increased risk of preterm birth or low birth weight compared with the general population (8). Immunosuppression, being one of chemotherapies side effects, has been observed to increase the risk for the conditions mentioned above (14), which are much more likely to occur to women who received chemotherapy or gave birth within two years of diagnosis (8).

In the for mentioned research (14) is described how the preterm birth risk was double, in comparison with women who had not been associated with a cancer diagnosis in the same time of birth, for chemotherapy without radiation and 2.4 times higher for chemotherapy with radiation. The highest risk for preterm birth and low birth weight was linked to pregnancies that started within one year of starting treatment. Conversely, the risk for a preterm infant, low-birth-weight infant or small for gestational age infant was the same to women with no cancer history if the pregnancy was conceived at least one year after starting chemotherapy without radiation, or two years or more, after chemotherapy with radiation. Last but not least, 3 out of 9 of women whose first pregnancy after treatment ended in stillbirth, had conceived within one year of starting chemotherapy.

A different study aiming to determine pregnancy outcome to women in Korea after treatment for breast cancer had the following findings: 992 women became pregnant out of 33,761 women included in the study. 622 (67.5%) out of 992 women who became pregnant had a successful delivery, while the remainder 370 women failed to deliver. Those who successfully delivered were younger (mean age 30.6 years vs. 33.9 years of those who failed to deliver) and had lower

frequencies of chemotherapy (29.4% vs 41.9%, $p=0.012$). Furthermore, they were more likely to have become pregnant >2 years after surgery for breast cancer treatment (17.7% vs 34.1%, $p<0.001$), compared with those who failed to deliver (16).

BRCA mutations

Pregnancy after breast a cancer diagnosis, even in patients with hormone-positive disease, is considered safe. Yet, data concerning women with BRCA mutations (12% of breast cancers in women younger than 40 years of age) are very limited. On those grounds, an international, multicenter, hospital-based, retrospective cohort study was conducted and the results presented favorable fetal outcomes. While 20 of 195 women experienced a miscarriage (10.3%) and 16 women undertook an abortion (8.2%), 150 women gave birth, and from the total of 170 neonates, pregnancy complications occurred in 13 (11.6%) and congenital anomalies in 2 (1.8%) of the cases (11).

Cryopreservation

The first live birth after cryopreserved oocytes associated with an oncologic indication was reported in 2007. Ter Welle-Butalid et al. (8) have summarized the results of studies concerning embryo cryopreservation. Even though the oncology indications were different, the purpose was fertility preservation. The number of women who actually had an embryo transferred after preceding oocyte preservation, ranged from 0-5%. Overall, 23% of 614 women underwent at least one embryo transfer and 40% of them had a live birth. It should be noted that return rates are influenced by the general advice to abstain from becoming pregnant for at least two years after diagnosis. It is understood that return rate depends on the longer or shorter observation time and other factors such as maintained ovarian function after chemotherapy or even reconsideration on family planning.

In recent studies, it has been revealed that pregnancy does not have a negative impact on prognosis (17). Knowledge about the different options of fertility preservation is expanding. The relatively new technique of cryo conservation of ovarian cortex shows promising results, but data of long-term follow-up remain necessary. Besides, the appropriate interval between cancer and the following pregnancy needs to be defined. Improvements in local and systemic treatment, along with earlier diagnoses through breast awareness and screening, have led to increases in survival and a decline in breast cancer (BC) recurrence. Women with BC should be informed about the subsequent adverse effects of BC and its treatments on conception. With the increasing trend for women to defer childbirth to later in life, provision of fertility-related information, access to fertility preservation, and fertility-related psychosocial support should be offered to women of a reproductive age before they begin BC treatment (18). When proven fertility preservation methods are not feasible, and in the setting of young women with breast cancer, GnRHa may be offered to patients in the hope of reducing the likelihood of chemotherapy-induced ovarian insufficiency. GnRHa should not be used in place of proven fertility preservation methods (19).

An improvement in the survival rates of cancer patients and recent advancements in assisted reproductive technologies have led to remarkable progress in oncofertility and fertility

preservation treatments. Currently, for adults and post-pubertal girls, oocyte or embryo cryopreservation is an established method. The field of ovarian tissue cryopreservation is advancing quickly and may evolve to become standard therapy in the future (20).

Nowadays, giving hope for a family after cancer diagnosis and treatment should be considered a crucial ambition in cancer care. Therefore, oncofertility care has become a priority and a mandatory component of the management of young women with newly diagnosed breast cancer. Increased awareness by all health care professionals in oncology is needed to make sure this topic is always discussed at diagnosis and women can make fully informed decisions about the proposed anticancer therapies and their potential interest in accessing the available strategies for ovarian function and/or fertility preservation. (21).

CONCLUSION

Breast cancer is the most common type of cancer occurring to women of reproductive age. Pregnancy after breast cancer is actually still a rare entity but the incidence is increasing. Thus gynecologists, obstetricians, and oncologists may be confronted with this complex situation more often and should be familiar with the management possibilities. Women can therefore be reassured and interruption of pregnancy is not generally indicated. Women who intend to get pregnant after a diagnosis of breast cancer, also need special information. It has now grown to be clear that becoming pregnant after treating breast cancer is safe. There are ways of preserving fertility during the treatment, such as oocytes and/or embryo cryopreservation. Pregnancy is contraindicated for at least two years after chemotherapy and radiation treatment completion or for one year after chemotherapy treatment completion, since this timing of conceiving showed more promising pregnancy outcomes.

Preterm birth, low-birth-weight neonates or small for gestational age neonates, were associated with becoming pregnant within one year of starting breast cancer treatment. Counseling on childbearing should be provided before the initiation of breast cancer treatment and women should be informed about all the available choices for preserving their future ability to gestate.

A number of options are available to preserve fertility in female BC patients, and these fertility preservation procedures should be discussed and preferably introduced, before the patient starts systemic therapy. A patient's age at diagnosis, the type of adjuvant treatment given, time available before the start of treatment, and the delay in childbearing required after treatment should be considered when counseling patients about the effects of treatment. Clinicians should provide patients with support and detailed information regarding the reproductive risks after BC treatment to improve their overall physical and emotional recovery. Women with breast cancer welcome the option to discuss and explore the fertility and pregnancy options available to them prior to commencement of their treatment.

In fact, this is essential to promote women's well-being and can increase treatment compliance later on. Additional age-related issues should be considered when managing breast cancer in young women and effective communication is at the

forefront of this approach. Health professionals working with women diagnosed with breast cancer, should be encouraged to approach fertility issues at the outset of cancer treatment. Early referral of patients with breast cancer and incomplete family planning to a specialist, to discuss fertility preservation options, is of paramount importance to female cancer patients.

Building a positive rapport surrounding this issue can help and facilitate each individual woman's cancer journey. Considering the rising trend in delaying childbearing and the suboptimal knowledge of health care providers towards these survivorship issues, further awareness and education towards enhancing the oncofertility counseling of young women with breast cancer need to be prioritized.

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