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FERTILITY ISSUES AND BREAST CANCER (J JERUSS, SECTION EDITOR)

# Impact of Breast Cancer Systemic Therapies on Fertility

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## Abstract

**Purpose of Review** Many young women diagnosed with breast cancer will be confronted with premature ovarian insufficiency and infertility as a consequence of systemic therapies used to treat their cancer. This is a concern for nearly half of young women diagnosed with breast cancer. We will review the impact of breast cancer chemotherapy, endocrine therapy, and immunotherapy on fertility and surrogate markers of fertility.

**Recent Findings** Modern breast cancer treatments continue to have an impact on a woman's fertility potential. This risk is reduced as more patients are able to safely eliminate chemotherapy as part of their treatment plan without compromising cancer-related outcomes. Research is being done to assess whether patient outcomes are affected from pausing endocrine therapy to allow for pregnancy.

**Summary** With varying extent, most breast cancer treatments have some impact on fertility although more data is necessary. Individualized fertility counseling is an important aspect of comprehensive cancer care. This review highlights the special population of premenopausal breast cancer patients and the challenge in their care should they desire children.

**Keywords** Fertility · Premenopausal · Amenorrhea · Breast cancer · Adjuvant

## Introduction

Nearly 7% of women with breast cancer are diagnosed prior to the of age 40 [1]. Fertility and pregnancy are concerns for approximately half of young women diagnosed with breast cancer as many will face premature ovarian insufficiency and infertility as a consequence of systemic therapies used to treat breast cancer [2, 3••]. A fertile 30-year-old woman has a 20% chance of pregnancy per cycle, whereas a 40-year-old woman has less than a 5% chance of pregnancy per cycle [4]. These important concerns during a time when fertility declines can impact quality of life as well as treatment decisions, adherence to endocrine therapy, and possibly survival [5]. As a result, individualized fertility counseling is an important aspect of comprehensive cancer care for young women with breast cancer.

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There are a number of different systemic therapies used in the adjuvant treatment of breast cancer (Table 1). We will review the impact of breast cancer chemotherapy, endocrine therapy, and immunotherapy on fertility and surrogate markers of fertility including menstrual patterns and ovarian reserve markers.

## Chemotherapy

For years, chemotherapy has been the mainstay of breast cancer treatment. Breast cancer is considered a systemic disease with microscopic dissemination at the time of diagnosis. The risk of bone marrow micro-metastasis in breast cancer has been established, even in very small, low grade, and lymph node negative cancers [6]. Chemotherapy for the treatment of breast cancer dates back to the early 1970s, when the first report on the efficacy of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) as adjuvant treatment of breast cancer was described [7]. For many years, the majority of patients with breast cancer, regardless of stage, received some form of chemotherapy [8]. The turn of the century boasted the development of gene expression profiling which enlightened the fact that not all breast cancers are the same [9]. Over the years,

**Table 1** Common systemic agents used for the adjuvant treatment of breast cancer

| Alkylating agents | Cyclophosphamide |
|---|---|
| Anthracyclines | Doxorubicin<br>Epirubicin |
| Taxanes | Paclitaxel<br>Docetaxel |
| Platinum | Carboplatin |
| Endocrine therapy | Tamoxifen<br>Letrozole<br>Exemestane<br>Anastrozole |
| HER2-directed therapy | Trastuzumab<br>Pertuzumab<br>Ado-trastuzumab emtansine<br>Neratinib |

both the agents used in breast cancer and the treatment schedules for breast cancer have evolved. Alkylating agents, anthracyclines, and taxanes have long been considered, and remain, the most commonly used chemotherapy agents.

In this section, we will review the common chemotherapy agents and their combinations used for the systemic treatment of breast cancer, with a particular focus on their impact on fertility.

## Alkylating Agents

Alkylating agents, such as cyclophosphamide, contribute significantly to ovarian toxicity and menopause. Alkylating agents are non-cell cycle dependent and work by causing direct DNA damage to the cells and thus can affect both actively dividing cells and non-active oocytes and pre-granulosa cells [10, 11]. In an analysis of more than 2500 women treated for breast cancer with an alkylating agent, specifically with the regimen CMF, the risk of treatment induced amenorrhea was 40% for women ≤ 40 years of age and 76% for women 41 years of age or older [12]. Other cyclophosphamide containing regimens, such as CEF (cyclophosphamide, epirubicin, 5-flurouracil) and CAF (cyclophosphamide, doxorubicin, 5-flurouracil), appear to be even more gonadotoxic, with studies reporting treatment-related amenorrhea rates at 1 year of 40–50% in women of ≤ 40 years of age and 90–100% in women of ≥ 41 years of age [13]. Older age is a risk factor for treatment-related amenorrhea after alkylating chemotherapy for breast cancer [14].

More modern chemotherapy regimens use other chemotherapy classes, such as anthracyclines and taxanes. In a trial comparing doxorubicin (A) and docetaxel (T) to regimens with cyclophosphamide (either AC + T or TAC), rates of treatment-related amenorrhea were lower in the cohort of patients who did not receive cyclophosphamide (C) [15]. The cumulative dose of cyclophosphamide received may also influence fertility outcomes. Anthracycline-based regimens usually combine an anthracycline with a lower dose alkylating agent (AC), and thus, there is a lower risk of premature ovarian failure [16, 17].

## Anthracyclines

Anthracycline agents have proven to be very active in breast cancer, and their use has led to the replacement of older regimens such as CMF [18]. The role of anthracycline agents in breast cancer continues to evolve due to its toxicity profile, namely, cardiotoxicity and secondary leukemias.

While the effects of anthracyclines alone on fertility are unknown, data shows that there is a lower risk of treatment-related amenorrhea with anthracycline-containing regimes, such as doxorubicin and cyclophosphamide (AC) or 5-flurouracil, epirubicin, and cyclophosphamide combinations (FEC/CEF). This difference may be driven by the fact that the cumulative dose of cyclophosphamide in these regimens compared with standard CMF is lower [17, 19]. In an observational study of women with breast cancer who received chemotherapy and conceived spontaneously, regimens with anthracyclines were associated with a greater probability of pregnancy compared with a taxane-containing regimen [20]. Outside of the context of breast cancer, where women receive anthracycline agents without an alkylating agent, such as in Hodgkin's lymphoma, there was no significant increase in premature menopause or infertility [21, 22]. This may suggest that the gonadotoxic effects of anthracyclines are minimal, especially when compared to alkylating agents.

## Taxanes

The risk of ovarian toxicity associated with taxanes is not well defined. In a landmark trial by Martin et al., the role of taxanes in adjuvant breast cancer treatment was established [23]. Docetaxel plus doxorubicin and cyclophosphamide (TAC) was compared to 5-fluorouracil plus doxorubicin and cyclophosphamide (FAC) as adjuvant chemotherapy for operable, node-positive breast cancer. While TAC demonstrated a superior disease-free survival and overall survival, this was at the cost of a higher rate of amenorrhea (61.7% versus 52.4%, $p = 0.007$).

More contemporary regimens give taxanes sequentially rather than concurrently with AC. A small retrospective study of chemotherapy-induced amenorrhea concluded that sequential taxanes do not increase the risk of chemotherapy-induced amenorrhea when given after AC [24].

In contrast, a retrospective study by Tham et al. showed that the risk of permanent amenorrhea with AC followed by T versus AC alone was increased, particularly in women over the age of 40 [25]. A different sequential taxane regimen,

FEC-Doc (fluorouracil, epirubicin and cyclophosphamide followed by docetaxel), has been studied but is not commonly used in practice. One study showed that the anti-mullerian hormone (AMH), a surrogate marker for ovarian reserve, declined rapidly in 98% of women who received a FEC-Doc and showed no signs of recovery at 2 years post-treatment in 73% of women, though only 50% of women experienced chemotherapy-induced amenorrhea [26]. It should be noted that AMH is not routinely tested in premenopausal women receiving systemic breast cancer treatment and more data is needed to guide its use in predicting fertility after chemotherapy.

A small study suggested that docetaxel had a higher risk of treatment-related toxicity than paclitaxel; however, most studies group docetaxel and paclitaxel together; thus, data supporting the use of one taxane over another for the purpose of fertility preservation in premenopausal women is limited [14]. Overall, data for the independent risk of taxane-induced ovarian toxicity are conflicting, although the common themes are that the risk is increased with age and when given in combination with an alkylating containing regimen [17, 27–30].

### Platinum Agents

Platinum agents are being increasingly used in breast cancer, specifically in "triple negative" and human epidermal growth factor receptor 2 (HER2) positive disease. There is limited data in regard to the effect of platinum agents on fertility. A retrospective study by Gast et al. assessed chemotherapy-related amenorrhea in a variety of different chemotherapy regimens, including doxorubicin/cyclophosphamide followed by paclitaxel (AC-T) or docetaxel/carboplatin (TC) [31••]. TC was associated with less chemotherapy-related amenorrhea than AC-T. A different study with HER2 positive patients found that TC with trastuzumab (TCH) had a higher rate of treatment related amenorrhea compared to anthracycline-based therapy; however, post-treatment menopausal status was assessed earlier in the TCH group than the anthracycline-based group; thus, the authors in this study noted that this conclusion should be interpreted with caution [32]. Nonetheless, neither of these studies clarify the risks of platinum agents alone.

## Endocrine Therapy

With the advent of precision medicine, fewer patients are requiring chemotherapy to achieve the same clinical outcome. Genomic testing tools, such as Oncotype DX, MammaPrint, and PAM50, to name a few, have been valuable in identifying those patients whose risk of breast cancer recurrence is low, and thus adjuvant chemotherapy can be eliminated without compromising survival outcomes [33–35]. These tools are particularly useful in hormone receptor positive breast cancers, in which hormone blocking therapies, also known as endocrine therapy, can be used as an alternative and less toxic form of systemic therapy. Hormone receptor positive (estrogen receptor positive ± progesterone receptor positive) breast cancers represent more than 70% of all breast cancers and are often associated with a good prognosis [36]. Two-thirds of premenopausal women will have estrogen receptor positive tumors, although it should be recognized that premenopausal women are more likely to be estrogen receptor negative compared to post-menopausal women [37]. In this section, we will discuss the effects of endocrine therapy on fertility.

### Tamoxifen

Tamoxifen, a selective estrogen receptor modulator, is part of the adjuvant treatment of hormone receptor positive breast cancer. It can be used after chemotherapy or alone, depending on the clinical setting and patient's recurrence risk. It is well established that tamoxifen has teratogenic effects on the development of the fetal reproductive tract, but its impact on fertility is less clear [38]. At higher doses, tamoxifen can act like the fertility drug clomiphene and actually stimulate ovulation [39]. However, tamoxifen can cause irregular or absent menses in patients. When used after chemotherapy, tamoxifen was associated with a 2-fold increased risk of treatment-related amenorrhea [17]. When used alone, the risk of amenorrhea in women less than age 40 was negligible [40]. Most studies have shown that tamoxifen-induced amenorrhea is transient and reversible [17, 41].

One of the challenges with endocrine therapy in relation to future fertility is the duration of treatment. In premenopausal women, it is recommended that adjuvant endocrine therapy be continued for at least 5 to 10 years. This recommendation comes from two large trials which demonstrated that continuing tamoxifen beyond 5 years decreased breast cancer recurrence and mortality [42, 43]. Pregnancy is not advised while a patient is on tamoxifen; however, due to the extended duration of recommended therapy, a woman may miss the opportunity to have a biologically related child. Hershman et al. found that women under the age of 40 had the highest risk of early discontinuation of tamoxifen [44]. Fertility concerns are one of the most common reasons for noncompliance with tamoxifen [5]. While there are no prospective data to comment on patient outcomes when tamoxifen is temporarily held for the purposes of pregnancy, there is evidence that suggests pausing tamoxifen to allow for pregnancy does not negatively impact patient survival [45].

### Aromatase Inhibitors

An alternative endocrine therapy regimen for premenopausal women with hormone receptor positive breast cancer is the

combination of an aromatase inhibitor (AI) and a mode of ovarian function suppression (OFS examples include GnRH agonist, oophorectomy, ovarian irradiation). This is favored over tamoxifen in premenopausal women who are considered "high risk" as demonstrated in the SOFT/TEXT trials [46]. By further decreasing endogenous estrogen exposure in this high risk population, there was improved disease-free survival. "High risk" usually refers to those patients in whom chemotherapy was recommended or who were under the age of 35. Undoubtably, a woman receiving an AI with OFS cannot become pregnant. In contrast to tamoxifen, this combination will put the patient into menopause. It is not known whether a treatment break from AI + OFS will result in resumption of menses or how this will impact breast cancer-related outcomes. The POSITIVE trial (NCT02308085), a prospective study that recently met accrual, seeks to assess safety of a hiatus from endocrine therapy to allow for pregnancy in hormone receptor positive patients [47•].

### Fulvestrant

Fulvestrant is an estrogen receptor agonist that can be used in the treatment of metastatic hormone receptor positive breast cancer. It currently does not have a role in the adjuvant treatment of women with hormone receptor positive breast cancer, and it is not known whether fulvestrant can cause fetal harm or adversely affect reproductive capacity in humans.

## Immunotherapy and Targeted Therapies

### Anti-HER2 Therapy

HER2-directed therapy is used exclusively in HER2 positive breast cancers. Dating back to the early 1990s, trastuzumab, a monoclonal antibody directed against the HER2 extracellular epitope, changed the face of breast cancer treatment by showing a 5-month improvement in survival for patients with metastatic HER2 positive breast cancer [48]. Trastuzumab was later approved for the adjuvant setting in 2005 [49]. Trastuzumab is contraindicated during pregnancy due to its risk of causing oligohydramnios. Little is known about the effects of trastuzumab on fertility. In a study of women with small HER2 positive breast cancers, in which subjects received paclitaxel with trastuzumab, treatment-related amenorrhea occurred in 28% of the premenopausal women; however, all but one were over the age of 40 [3••]. How much of this was driven by paclitaxel versus trastuzumab is unknown. Abusief et al. reported that the addition of trastuzumab has not been associated with treatment-related amenorrhea in patients who received AC ± T [50]. Interestingly, in a cross-sectional study evaluating AMH in premenopausal chemotherapy-treated breast cancer survivors and control patients, trastuzumab was associated with increased AMH in women with normal cycles [51]. Similar findings were seen in another small observation study suggesting lack of gonadotoxicity associated with trastuzumab [52•].

Pertuzumab is another monoclonal antibody that binds to a different HER2 epitope from trastuzumab and inhibits HER2 dimerization necessary for downstream signaling and cell growth. Similar to trastuzumab, animal models have shown that pertuzumab can cause oligohydramnios during pregnancy. There are no studies that have been performed to assess the impact of pertuzumab on fertility. In animal studies for pertuzumab, however, there were no reported adverse effects on reproductive organs [53]. Neratinib, an oral small molecule inhibitor of HER1, HER2, and HER4, also lacks human data on its effects on fertility.

Ado-trastuzumab emtansine (TDM-1) is an antibody drug conjugant that directly delivers the microtubular inhibitor DM1 to HER2 positive cells. Patients with HER2 positive breast cancer who have residual disease at the time of surgery after they have received neoadjuvant chemotherapy + trastuzumab can receive TDM-1 based on findings from the landmark KATHERINE trial [54]. The impact of TDM-1 on fertility was assessed in an exploratory analysis of the phase II ATEMPT trial in which toxicities were compared between patients who received TH (paclitaxel and trastuzumab) or TDM-1 for stage 1 HER2 positive breast cancer. While this was a small study, the rate of chemotherapy related amenorrhea was lower in those patients who received TDM-1 [55].

Other immunotherapeutic agents, such as immune checkpoint inhibitors, are just recently making their way into the (neo) adjuvant setting for the treatment of breast cancer [56]. Immune checkpoint inhibitors, like pembrolizumab, do not appear to have a clear impact on fertility; however, hypophysitis is a rare, but known toxicity which could potentially disrupt the hypothalamus-pituitary-adrenal axis and subsequently cause infertility.

## Special Considerations

GnRH agonist co-treatment during chemotherapy has been proposed for ovarian protection. Chemotherapy induces apoptosis of developing ovarian follicles leading to a decline in estradiol and inhibin B, which provide negative feedback signals to the hypothalamus and pituitary. In response, the pituitary increases secretion of follicle-stimulating hormone (FSH), which drives follicular recruitment. As recruited follicles undergo chemotherapy-induced apoptosis, ovarian reserve declines at an accelerated pace. GnRH agonists have been hypothesized to preserve ovarian reserve through several mechanisms. Depot GnRH agonist induces downregulation of FSH production 7–10 days post-administration, which leads

to suppression of the hypothalamic-pituitary-ovarian axis. The lower circulating levels of FSH diminish the accelerated loss of ovarian reserve mediated by FSH-driven follicular recruitment. GnRH agonists may also protect the ovaries by decreasing ovarian perfusion, reducing delivery of the chemotherapeutic agent to the ovaries.

Goserelin and triptorelin are the GnRH agonists most often used in recent ovarian protection studies in breast cancer patients, while buserelin and leuprolide have been used in studies published in the 1980s and 1990s, as well as in patients with hematologic malignancies. Side effects of GnRH agonists are related to the induced hypoestrogenic state and include hot flashes, vaginal dryness, and bone loss. Norethindrone acetate is a progestin with estrogenic properties that has been shown to preserve bone mass and significantly reduce vasomotor symptoms without increasing the rate of vaginal bleeding. Add-back therapy with norethindrone would not be appropriate in women with hormone receptor positive breast cancer.

With respect to the safety of GnRH agonist co-treatment, multiple studies have concluded that chemotherapy-induced amenorrhea results in improved disease-free and overall survival in women with breast cancer. Given the possible survival benefit associated with premature ovarian insufficiency, trials of GnRH agonists have examined disease-free and overall survival of participants to determine if ovarian protection alters these important outcomes. In the Prevention of Early Menopause Study (POEMS), women with hormone receptor negative early breast cancer were randomized to co-treatment with goserelin versus chemotherapy alone [57]. Women with hormone receptor negative early breast cancer were studied to eliminate the confounder of tamoxifen use. Despite closing the trial early due to funding issues, a reduction in premature ovarian failure was observed with goserelin co-treatment. In addition, a non-significant trend toward disease-free survival, as well as a significant increase in overall survival, was observed in the goserelin group, suggesting safety of GnRH agonist co-treatment in women with triple-negative cancer. A possible explanation for this finding is that luteinizing (LH) receptors are frequently present in triple-negative cancers. Preclinical studies have shown that the use of GnRH analogs in xenograft models of triple-negative breast cancer is associated with growth inhibition, reduction in metastasis, and apoptotic cells. It is possible that the GnRH agonist co-treatment may contribute to obtaining remission and it does not appear that ovarian protection is harmful for disease-free survival or overall survival among women with triple-negative breast cancer.

Given the challenge of conducting research that is powered to compare and track long-term outcomes such as fertility, there are limited randomized data on fertility-related outcomes such as fecundity, miscarriage rate, and maternal and neonatal outcomes after co-treatment with a GnRH agonist during chemotherapy. As a result, most GnRH agonist co-treatment studies are designed to show a difference in the rate of resumption of menses or the rate of premature ovarian insufficiency 1–2 years after chemotherapy. To date, at least 11 randomized controlled trials have been published on co-treatment with a GnRH agonist or chemotherapy alone in women with breast cancer. A recent meta-analysis found that the rate of premature ovarian insufficiency was 14.1% in the group that received GnRH agonist co-treatment and 30.9% in the control group (adjusted odds ratio, 0.38; 95% CI, 0.26 to 0.57; $p < .001$). A total of 37 (10.3%) patients had at least one post-treatment pregnancy in the GnRH group and 20 (5.5%) in the control group (incidence rate ratio, 1.83; 95% CI, 1.06 to 3.15; $p = .030$). No differences in disease-free survival (adjusted hazard ratio, 1.01; 95% CI, 0.72 to 1.42; $P = .999$) and overall survival (adjusted hazard ratio, 0.67; 95% CI, 0.42 to 1.06; $p = .083$) were observed between groups. Several criticisms of the individual trials and the meta-analysis exist. First, several trials enrolled women in their mid- to late 40s. Given the high rates of infertility and natural menopause in this population, fertility outcomes could not be directly assessed. The chemotherapy regimens used in the trials performed 20–30 years ago typically included higher cumulative doses of cyclophosphamide and were more ovarian toxic than current regimens that use lower cumulative doses of cyclophosphamide. This resulted in heterogeneity of the chemotherapy regimens in the meta-analysis. Several trials include women with hormone-positive cancers that are typically treated with tamoxifen after chemotherapy, and some do not provide information on hormone receptor status and treatment with tamoxifen. Tamoxifen is considered a confounder as it can be associated with amenorrhea, as described in earlier sections. The definition of premature ovarian insufficiency varies between trials. Some studies base the diagnosis solely on patient-reported amenorrhea lasting greater than 6–12 months, whereas others included FSH values in the diagnosis. Finally, most studies were powered to show a difference in the rate of premature ovarian insufficiency and not fertility outcomes. Of note, several studies were stopped prematurely because of a lack of a benefit noted at the interim analysis. Information on how participants were tracked for fertility outcomes is limited in most of the trials, thus limiting the ability to objectively assess differences for these endpoints.

While women with breast cancer who are co-treated with an GnRH agonist during chemotherapy may experience a 38% reduction in the risk of premature ovarian insufficiency, neither the American Society for Reproductive Medicine (ASRM) nor the American Society of Clinical Oncology (ASCO) recommends GnRH agonist co-treatment as a primary means of fertility preservation, possibly due to the limited efficacy and limitations in the data [58, 59]. Both societies recommend that GnRH agonist co-

treatment be offered as a means of fertility preservation in addition to, but not in place of, oocyte, embryo, or ovarian tissue cryopreservation.

## Future Directions

There remain large gaps in knowledge in regard to the impact of systemic breast cancer therapies on fertility and pregnancy outcomes. Patients who wish to become pregnant are faced with uncertainty when it comes to the ability to become pregnant, impact of current or prior treatment on the fetus, and their breast cancer outcomes. There has been a significant interest in prospectively evaluating these concerns further. In the recently accrued Pregnancy Outcome and Safety of Interrupting Therapy for Women With Endocrine Responsive Breast Cancer (POSITIVE) trial, women age 42 and younger receiving endocrine therapy for a diagnosis of breast cancer for at least 18 months and no more than 30 months were enrolled [47•]. Those enrolled in the trial will take a planned break in treatment (for at least 3 months prior to attempting to conceive) for up to 2 years to allow for pregnancy. After pregnancy, delivery, and breastfeeding (if desired) or up to the 2 years of attempting to conceive, subjects will resume their planned endocrine therapy for the duration of the recommended treatment. The study recently completed accrual of over 500 patients, and this will help add to the understanding of how to guide women desiring pregnancy while on endocrine therapy, particularly with the more extended duration of therapies recommended.

Similarly, the MotHER trial seeks to answer similar questions in patients receiving trastuzumab and/or pertuzumab and is the first prospective study of the effects of a targeted cancer therapy on pregnancy outcomes [60].

Targeted therapies are being studied and developed for the adjuvant treatment of breast cancer at a rate never seen before. The paucity in knowledge of the effects of these novel therapies on fertility will continue to grow highlighting an unmet need for our patients.

## Conclusion

Modern breast cancer treatments continue to have an impact on a woman's fertility potential. This risk is somewhat reduced as more patients are able to eliminate chemotherapy as part of their treatment plan due to genomic testing. Research is being done to assess whether patient outcomes are affected from pausing endocrine therapy for the purpose of pregnancy. As more breast cancer agents are developed, the knowledge gap of the impact on fertility widens. This review highlights the special population of premenopausal breast cancer patients and the challenge in their care should they desire children.

## Compliance with Ethical Standards

**Conflict of Interest** Bahar Moftakhar, Wendy Vitek, and Alissa Huston declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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