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BREAST CANCER (B OVERMOYER, SECTION EDITOR)

Issues with Fertility in Young Women with Breast Cancer

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Abstract

Purpose of Review There are competing risks and benefits of cancer therapies and fertility preservation in young women with breast cancer. Here we discuss the impact of therapy on fertility, fertility preservation options, and emerging information in fertility issues for the breast cancer patient.

Recent Findings All systemic forms of breast cancer treatment can impact future fertility. Pre-therapy fertility preservation may offer the best opportunity for future fertility. Shared decision making with the individual patient and clinical scenario is important. Early referral to a fertility specialist should be offered to young patients.

Summary We find that fertility preservation options for young women diagnosed with breast cancer are currently available, but potentially under-utilized. We conclude that a multidisciplinary approach is necessary, with discussion of potential risks and benefits of fertility preservation options in the context of the patient's clinical disease.

Keywords Breast cancer · Fertility preservation · IVF · Premenopausal breast cancer · BRCA

Introduction

The treatment of young women with breast cancer presents unique and complex issues. As women delay pregnancy for personal and professional reasons, the diagnosis of breast cancer may occur prior to the completion of childbearing in young women. Although the incidence of breast cancer in the premenopausal woman is increasing, the overall prevalence is low [1, 2]. Only 1% of women with breast cancer are diagnosed before age 30 years, with 6.6% diagnosed before age 40 years [3]. Young women who present with breast cancer frequently present with advanced stages of disease that are likely secondary to the fact that routine screening is not recommended in women under 40 years of age. Additionally, delays in diagnosis are common, as breast cancer is not high on the differential when a young woman presents with a breast mass.

Young women are also more likely to present with aggressive molecular subtypes of breast cancer, such as triple negative (TN) and HER2-positive breast cancer [4, 5]. When matched for stage and tumor characteristics, age is an independent prognostic factor that is associated with worse disease-specific and overall survival [6, 7]. However, even with worse outcomes compared to older women, many young women survive breast cancer with modern therapeutic paradigms [3]. In addition, there are several unique characteristics of young women who present with breast cancer, including the higher rate of germline mutations, such as *BRCA*, which deserve special consideration. Carriers of *BRCA* and other genetic mutations may have additional issues related to fertility preservation.

Fertility preservation refers to the efforts to help women with cancer retain their fertility, or with their ability to procreate. Cytotoxic chemotherapy, endocrine therapy, and ovarian suppression are all common breast cancer treatments that can significantly decrease or delay a woman's ability to become pregnant after completion of treatment. Many of these modern therapies directly impact a woman's fertility and include recommendations to delay pregnancy for an additional period of time (usually 2 years) after completion of treatment [8–10]. Further, there has been a trend in delay of childbearing on a societal level, which can add to fertility-related concerns.

At the time of diagnosis, discussion of a woman's desire in fertility preservation is crucial. Early referral to a reproductive endocrinologist is a critical step to assist women with breast cancer who would like to pursue future childbearing.

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Counseling about the impact of various treatments on fertility is also recommended. Multiple options for fertility preservation exist and are associated with some risks and uncertainties. These may include delays in breast cancer treatment and costly expenses. It has been reported that women are willing to alter their therapeutic course in order to pursue pregnancy [11]. Further research is necessary to evaluate the impact of specific fertility protocols on breast cancer safety, as well as its impact on pregnancy success rates. Currently, standardized protocols for ovarian stimulation are not available, and some protocols may theoretically be considered risky, particularly for women with estrogen receptor (ER) positive breast cancer, as they may increase endogenous estrogen levels.

It is critical to understand the competing risks and benefits of cancer therapies and fertility preservation in young women with breast cancer. In this review, we discuss the impact of therapy on fertility, fertility preservation options, and emerging information in fertility issues for the breast cancer patient.

Impact of Breast Cancer Treatment on Fertility

Cytotoxic Chemotherapy

Ovarian function and the absolute number of oocytes define a woman's reproductive time span. A woman's absolute number of oocytes decline over time. Cytotoxic chemotherapy can cause injury and toxicity to all ovarian cells leading to chemotherapy-induced amenorrhea [12]. The rate of chemotherapy-induced amenorrhea increases with a woman's age (as a reflection of the natural loss of oocytes), and depends on the specific regimen of chemotherapy used. Rates can be as low as 6% in extremely young women, but can be > 80% in women over 40 years of age [13]. Amenorrhea can be temporary, with some women regaining normal menses at 6 months after therapy [14]. Chemotherapy can permanently injure the ovary in multiple ways, from fibrosis of the organ to vascular damage and cell apoptosis [15, 16]. This damage can lead to premature ovarian failure, infertility, and early menopause.

Cytotoxic chemotherapy regimens used in breast cancer confer different degrees of toxicity to the ovary, and therefore risk of amenorrhea and premature menopause. Alkylating agents (cyclophosphamide) have the highest ovarian toxicity, with an inverse toxicity relationship with age (i.e., lower doses of alkylating agents can cause ovarian toxicity with increasing age) [13]. The timing of different chemotherapy regimens is hypothesized to impact the risk of amenorrhea, but there are no trials investigating specific schedules. In combination with other chemotherapeutic agents, alkylating agents can be even more toxic, with amenorrhea reported in 40–50% of patients [17]. Anthracycline-containing regimens also confer significant risk of toxicity to the ovary, with one-third of women reporting amenorrhea [18]. Women with *BRCA* mutations may benefit from platinum-based chemotherapy regimens. Although, platinum-based chemotherapies have a lower rate of amenorrhea compared to alkylating agents, there is still a significant risk [19].

Ultimately, the most commonly prescribed drug combination of cyclophosphamide, anthracycline, and taxane likely confers the highest risk of amenorrhea compared to other regimens, although any combination of the above-mentioned drugs increases risk [20••]. There are no data that HER2-directed therapies impact ovarian function. However, HER2-directed therapy consists of at least 1 year of therapy, and because of congenital birth defects associated with these agents, pregnancy during the administration of anti-HER2 therapies is contraindicated [21]. The administration of HER2-directed therapy significantly contributes to a delay in pregnancy and childbearing.

Endocrine Therapy

While young women are more likely to have TN or HER2 amplified breast cancer, a large proportion of women have estrogen receptor positive (ER+) breast cancer [22]. Endocrine therapy has resulted in a significant increase in disease-free and overall survival for women with ER+ breast cancer. Standard of care in premenopausal women with ER+ breast cancer is tamoxifen (a selective estrogen receptor modulator [SERM]) for 5 years [23]. While 5 years of tamoxifen is considered to be standard of care, 2 randomized controlled trials (ATLAS and aTToM) have demonstrated that 10 years of tamoxifen therapy confers additional benefit in premenopausal women and is now commonly recommended [24, 25]. The extended timeline of tamoxifen treatment impacts a woman's ability to pursue fertility, given the fact that tamoxifen is contraindicated in pregnancy [26].

Suppression of ovarian function in addition to estrogen blockade for adjuvant therapy has been controversial. The suppression of ovarian function trial (SOFT) demonstrated that ovarian suppression or ablation (in addition to tamoxifen) did not improve the disease-free survival in the study population, compared with tamoxifen alone. However, a subset of women younger than 35 years of age receiving adjuvant chemotherapy and who did not undergo menopause within 8 months of completion of chemotherapy had improved disease-free survival with concomitant ovarian suppression [27, 28••]. The Tamoxifen and Exemestane Trial (TEXT) demonstrated the use of exemestane (an aromatase inhibitor [AI]) with ovarian suppression was associated with improved disease-free survival compared to tamoxifen with ovarian suppression [29, 30••].

Although endocrine-directed therapy is standard of care and associated with significant oncologic benefit, up to 40% of young women with breast cancer are interested in

interruption of endocrine therapy to pursue fertility [11]. The POSITIVE (Pregnancy Outcome and Safety of Interrupting Therapy for women with endocrine responsIVE breast cancer) trial is investigating oncologic outcomes with successful fertility recovery with a 2-year interruption of endocrine directed therapy [31].

Non-Pharmacologic Ovarian Suppression/Ablation

Ovarian suppression is a treatment strategy that can be pharmacologic or surgical. For women who would like to preserve fertility, pharmacologic suppression is preferred to surgical removal, as pharmacologic approaches are reversible [32]. For women with *BRCA* mutations, prophylactic bilateral salpingo-oophorectomy (BSO) is recommended for ovarian cancer risk reduction involving those age 35–40 years for *BRCA1* carriers, and for those age 40–45 years for *BRCA2* carriers and/or when childbearing is complete [33]. BSO is also an option for ovarian suppression in women who are not interested in fertility preservation.

Other Adjuvant Therapies

In addition to chemotherapy and endocrine therapy, surgery and radiation therapy are integral components of the care of women with breast cancer. Radiation therapy is recommended for young women undergoing breast-conservation therapy and after mastectomy for those at high risk of local recurrence. Internal scatter of radiation can lead to doses of 2.1–7.6 Gy to the ovary when the breast and regional nodes are targeted; however, radiation does not cause ovarian ablation until doses reach approximately 24 Gy [34]. Unless a woman is receiving radiation to the pelvis (as in the case of targeted treatment of metastatic disease), the radiation dose to the ovaries with routine breast cancer radiation therapeutic regimens should not significantly impact fertility.

Fertility Assessment and Referral

Many women are unaware of the impact of their treatment on their fertility [12, 35, 36]. In spite of the lack of knowledge, women are interested in how their breast cancer treatment will affect their fertility [37]. Early referrals to a reproductive endocrinologist are important not only for the woman's fertility desires but also to avoid delays in the administration of fertility-affecting chemotherapy [38]. A recent study reported 50% of premenopausal women diagnosed with breast cancer are interested in having children in the future, and thus early referral to reproductive endocrinologists facilitate these women's ability to receive assessment [39].

If the referral occurs after completion of chemotherapy, there are additional options to evaluate a woman's potential fertility. The regularity (or irregularity) of menses is not a reliable assessment of fertility. Laboratory testing of ovarian function can offer more precise information. Anti-Mullerian hormone (AMH) is the most sensitive test that can approximate the number of ovarian follicles and is predictive of amenorrhea [40, 41]. Follicle-stimulating hormone (FSH), luteinizing hormone (LH) estradiol, and inhibin B can also be used to assess ovarian function and reserve; however, there are limitations to their use, including the need to monitor these levels over time, and a lack of standardization in test timing and the predictive validity [12, 13]. Ultrasound examination of the ovaries can also be used to evaluate follicle count and ovarian volume, although ongoing research is needed to evaluate ultrasound's validity in predicting fertility in the post-chemotherapy breast cancer population [42].

Fertility Preservation Strategies

For women who want to maximize their success of fertility after treatment, pre-therapy fertility preservation interventions are available. Each of the below strategies has its risks and benefits.

Oocycte and Embryo Cryopreservation

In vitro fertilization (IVF) can be pursued by women with breast cancer. IVF is most successful when the process begins with multiple oocytes. Ovarian hyperstimulation is used to stimulate the ovaries to produce oocytes, which can then be harvested and preserved or used to create embryos, which can be preserved. There are multiple protocols for ovarian stimulation, which can either be used in sync with a woman's natural menstrual cycle, or can be initiated with a GnRH antagonist to minimize the cycle and delay therapy for as short a time as possible [43]. Fertility protocols often differ depending on which specialized IVF center is used.

Advantages of oocyte and embryo cryopreservation include use of standard IVF strategies. Disadvantages include the invasiveness of the procedure, which may cause delay in cancer treatment [44]. Furthermore, ovarian stimulation can cause promotion of growth in ER+ breast cancers via enhanced estradiol levels [45]. Some IVF protocols use tamoxifen or letrozole to avoid this potential issue, and case-control studies with long-term follow-up have not demonstrated an increased rate of breast cancer recurrence [46, 47••]. A recent systematic review of letrozole for ovarian hyperstimulation demonstrated adequate oocyte yield, low estradiol levels, and no effect on breast cancer recurrence rates. Limitations of this systematic review include the heterogeneity of the

studies included [48••]. Women interested in fertility options such as IVF can pursue surgical and radiation therapy treatments while undergoing IVF and thus avoid delay in the receipt of adjuvant chemotherapy [49].

Emerging Techniques

Multiple experimental techniques are being investigated for fertility preservation, including cryopreservation of ovarian tissue and ovarian suppression with the use of gonadotropin-releasing hormone (GnRH) analogs. These techniques have some advantages and disadvantages compared to oocyte and embryo cryopreservation. They do not require ovarian stimulation or a male partner, and can be used without delay in cancer treatment. However, studies investigating GnRH administration during chemotherapy to suppress ovarian function have not demonstrated consistent results [32]. Ovarian tissue cryopreservation is more invasive than other cryopreservation options, with a risk of possible malignant cell implantation. Additionally, it is only available at select centers [44]. Continued investigation about the relative success of these techniques is necessary.

Special Populations

Women with *BRCA* mutations and other genetic mutations pursuing fertility options after treatment for breast cancer have several other issues to consider. The first is the consideration for the recommendation for surgical oophorectomy after completion of childbearing or age 35–45 years, depending on the specific mutation [33]. This may impact the timing of when women may seek aggressive fertility interventions. There are some data that *BRCA* mutation carriers may develop fewer oocytes in response to ovarian stimulation compared to non-mutation carriers [50]. Additionally, women with *BRCA* mutations may have more fragile oocytes as a result of the role *BRCA* genes play in mismatch repair [51]. If oocyte retrieval and fertilization is successful, some women with *BRCA* mutations have the option to consider pre-implantation genetic testing of fertilized embryos and selection [52••].

Conclusions

In conclusion, fertility preservation options for young women diagnosed with breast cancer are currently available. A multidisciplinary approach is necessary, with discussion of potential risks and benefits of fertility preservation options. Early referral to a reproductive endocrinologist is recommended to allow women the options of these interventions.

Compliance with Ethical Standards

Conflict of Interest Nicole Christian and Mary L. Gemignani declare 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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