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Breast Cancer

Maintaining Fertility in Young Women with Breast Cancer

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Opinion statement

Breast cancer effects nearly 200,000 American women each year, with 9% of these women still in their childbearing years. For this subset of future survivors, the issue of fertility may be a significant quality-of-life concern. Both the causes and treatments for infertility in young breast cancer patients must be thoroughly understood by the multidisciplinary team caring for these women in order for the caregivers to be effective advocates for their patients. Radiation, cytotoxic chemotherapy, and hormonal therapy all effect ovarian function to greater or lesser degrees, with the incidence of permanent post-treatment amenorrhea following systemic treatment for breast cancer in women age 50 or younger estimated as between 33% and 76%. The science of fertility preservation continues to experience significant advances in terms of the success of oocyte, embryo, and ovarian tissue preservation, and it is crucial that physicians and patients are aware of the available fertility preservation options. The optimal time to address the possibility of treatment-related infertility and strategies to combat this with younger patients is prior to treatment, rather than after cancer therapy has begun, and a full knowledge of the available technologies is a prerequisite for an informed discussion. Causes of ovarian suppression and options for treatment, including consideration of preimplantation genetic diagnosis and alternative parenting approaches are also discussed to assist the clinician caring for young patients with cancer.

Introduction

As screening and treatment for breast cancer improve, a growing population of young survivors is facing quality-of-life issues, including the prospect of cancer or treatment-related infertility. The reported incidence of amenorrhea after systemic therapy for breast cancer varies widely, and is related to age, type, and cumulative dose of chemotherapy administered. The incidence of permanent amenorrhea following systemic therapy for breast cancer ranges from 33% to 76% [1, 2]. The direct effects of other therapies, such as radiotherapy and hormonal therapy on fertility are less well defined. Interest in the growing field of oncofertility has spurred new research in this important area of survivorship. While advances in oocyte, embryo and ovarian tissue preservation are crucial, so too are physician and patient awareness of the available fertility preservation options. Discussing strategies to preserve fertility is an integral part of preserving a young woman's

quality-of-life after cancer and also encourages the patient to have expectations for a cancer-free future [3•]. This review will examine the etiologies and scope of the problem of infertility after breast cancer therapy, and will explore currently available strategies for fertility preservation.

Background

- The American Cancer Society estimates that there will be 180,500 new cases of breast cancer in 2008 [4]. Of these patients, an estimated 16,150 are under the age of 45 [5]. For reproductive-age women, a large number of whom have either not contemplated or not completed their families, the diagnosis of breast cancer poses fertility concerns. Advances in breast cancer care, including early diagnosis and aggressive chemotherapy, have improved the life expectancy for young women, and have necessitated an increased emphasis on issues of survivorship, including family planning. The American Society of Clinical Oncology has highlighted the importance of healthy survivorship, and has recognized the preservation of fertility as an integral part of the care of patients with cancer [6]. In a survey of 757 young breast cancer patients, Partridge *et al*. found that 57% had substantial concerns about future fertility, and 29% reported that this concern influenced their decisions regarding treatment [7]. It is, therefore, important to address the possibility of treatment-related infertility and strategies to combat this with younger patients prior to treatment, rather than after cancer therapy has begun. Therefore, a successful strategy for fertility preservation, which balances life-preserving treatments with fertility-preserving options, must be made as part of the overall oncologic treatment plan from its inception.

Effect of radiation, cytotoxic chemotherapy, and hormonal therapy on fertility

Radiation

- Ovarian follicles are sensitive to damage from ionizing radiation, which may result in atrophy of the organ and reduced primordial follicle reserve [8]. While radiation therapy is commonly part of breast cancer treatment, the ovaries are typically spared significant toxicity from this modality. The fertility threat caused by radiation is related to several factors including patient age, dose and trajectory of radiation, and use of concurrent chemotherapy [9]. The total dose of radiation to the pelvis needed to increase the risk of premature ovarian failure (POF) is estimated at 20 Gy, with failure at lower doses in women 35 years of age and older [10, 11]. Pelvic radiation also exerts an effect on the uterus, causing changes in both the musculature and blood flow, which can lead to endometrial damage and a higher rate of obstetrical complications [12]. For patients receiving radiation treatment directed to the abdomen and pelvis, the risk of these complications is most pronounced when conception occurs <1 year after radiation therapy has been completed [13]. Of the 50 Gy delivered to the breast during standard whole-breast radiotherapy, only 2.1–7.6 cGy reaches the uterus through internal scatter, which is considerably less than the dose needed to induce POF or cause detrimental effects to the uterus [14, 15]. Because of this small but detectable radiation dose to the pelvis, pregnancy or harvesting of eggs for *in vitro* fertilization (IVF) should not occur

during radiotherapy for breast cancer, but should be possible after treatment is completed.

Cytotoxic chemotherapies

- The impact of chemotherapy for breast cancer on fertility is significantly affected by the patient's baseline ovarian reserve. Patients should undergo an initial fertility work-up which should include an assessment of ovarian function through blood testing [basal follicle-stimulating hormone (FSH), leutenizing hormone (LH), and estradiol]. Further, ultrasound-guided estimation of ovarian volume and antral follicle count can be used to estimate ovarian reserve [16]. Additionally, there is evidence that anti-Mullerian hormone (AMH) and inhibin B levels may correlate well with antral follicle count and may be more consistent markers of ovarian reserve [17, 18]. Knowledge of the patient's baseline fertility status prior to treatment will enable counseling specific to the patient's treatment-related fertility threat and help to guide decision-making regarding the patient's candidacy for any fertility sparing options.
- Patients requiring therapy with an alkylating agent, such as cyclophosphamide, have the highest risk of ovarian toxicity and menopause as a consequence of their treatment. In an analysis of more than 2500 patients treated for breast cancer with multiple cycles of alkylating agents, such as cyclophosphamide/methotrexate/5-fluorouracil (CMF), the risk of amenorrhea was 40% for women ≤40 years of age, and 76% for women 41 years of age and older [1]. Treatment with an anthracycline-based regimen, such as doxorubicin/cyclophosphamide (AC), utilizes an anthracycline along with a lower dose of the alkylating agent, and thus is associated with a lower risk of POF [19]. The risk associated with the addition of a taxane (T) is less well defined. In a study by Tham *et al.*, the incidence of permanent amenorrhea with AC followed by T vs AC alone was increased in women over 40 years of age. Younger women often resumed menstruation several months after treatment had completed, which suggests that age is one of the strongest predictors of chemotherapy-induced amenorrhea [2]. The effects of trastuzumab and bevacizumab, or newer epothilone agents such as ixabepilone, on fertility have not yet been rigorously evaluated.

Hormonal therapies

- The selective estrogen receptor modulator (SERM) tamoxifen has not typically been associated with cessation of ovulation. Furthermore, at higher doses, tamoxifen can act like the related compound and fertility drug clomiphene, to stimulate ovulation. Despite this, tamoxifen may cause irregular or absent menses in some patients when given after gonadotoxic chemotherapy or when used alone. While there is a 15% decrease in the odds of continuing menstrual cycles after the first 1–2 years of therapy, tamoxifen-induced amenorrhea is thought to be reversible and temporary [20, 21••].
- Tamoxifen use during pregnancy or while attempting to conceive is discouraged, as it has been associated with abnormalities in the development and function of the fetal reproductive tract and an

increased risk of mammary tumors in the offspring of animal models [22]. There are sparse reports in the literature regarding human pregnancy and tamoxifen, but the general opinion is that tamoxifen should not be taken during pregnancy or while attempting to conceive [23]. Though there are no prospective studies or class 1 data, indirect evidence suggests that anti-estrogen therapy with tamoxifen can be delayed to allow for pregnancy after surgery and radiotherapy for breast cancer have been completed, without negatively influencing patient outcomes [24, 25].

Current strategies for fertility preservation in the breast cancer patient

Ovarian suppression during chemotherapy

- For patients requiring chemotherapy, suppression of ovarian function through manipulation of the hypothalamic–pituitary–gonadal axis concurrent with systemic therapy has been postulated for preservation of ovarian function [26]. Destruction of follicles engaged in the maturation pathway by chemotherapeutic agents causes an increase in FSH secretion through a loss of negative feedback. This increase in FSH causes additional follicles to enter the maturation pathway, exposing them to the effects of cytotoxic therapy. This cycle can theoretically be interrupted by the administration of a gonadotropin-releasing hormone (GnRH) agonist that achieves reversible arrest of follicle mobilization and maturation preventing an increase in FSH concentration [27••]. The Southwestern Oncology Group is currently enrolling patients in a randomized trial of the GnRH agonist, goserelin, during treatment for hormone receptor-negative breast cancer to evaluate its effect on preserving fertility. The British OPTION trial is not only similarly designed, but also includes hormone receptor-positive patients. Recchia *et al*. studied 100 women receiving 1 year of goserelin therapy concurrent with their adjuvant treatment, and at a median follow-up of over 6 years found that 67% of patients recovered normal menses, including 100% of the women <40 years of age [28]. However, they reported only three pregnancies from this cohort. Other smaller studies and animal models appear to support these findings, though more human data are needed before this treatment can be recommended or endorsed.
- There is some concern regarding the impact of GnRH agonists on the efficacy of chemotherapy based on evidence that tamoxifen administered simultaneously with chemotherapy may decrease the effect of cytotoxic therapy [29]. This effect may be caused by a tamoxifen-mediated arrest of cancer cell proliferation which then decreases tumor cell sensitivity to chemotherapy. A similar effect may thus be seen with estrogen suppression via GnRH agonists [30]. Ultimately, ovarian suppression with GnRH agonists during chemotherapy as a method to preserve fertility remains a highly controversial topic. The American Society of Clinical Oncology recommends that women interested in this treatment receive it only in the context of an approved clinical trial due to insufficient evidence regarding both safety and efficacy [6].

In vitro fertilization and embryo cryopreservation

- The fertility preservation option with the most established scientific evidence and highest success rate is oocyte retrieval, IVF, cryopreservation of embryos, and later implantation after cancer therapies are completed. Cytotoxic chemotherapy treatment is delayed in order to permit a cycle of hormone stimulation and retrieval of oocytes, which may not be suitable or acceptable for all patients. There is also concern regarding the appropriateness of this method for women with hormonally responsive ER/PR-positive tumors. During ovarian stimulation, estrogen reaches supraphysiologic levels, often 10–20 times the levels seen in natural cycles, and there is the potential of stimulating hormone receptors on malignant cells [31]. Additionally, data suggest that estrogens can have an indirect mitogenic effect on hormone receptor-negative tumors, making hormone stimulation theoretically unfavorable for these patients as well [32]. Unstimulated, or natural cycle, oocyte retrieval is possible, but the yield is often too low to justify the procedure and expense. An interesting alternative is controlled ovarian stimulation (COS) with either tamoxifen or an aromatase inhibitor given along with standard fertility medications. Tamoxifen for a short course at a dose of 40–60 mg daily results in the generation of a greater number of mature oocytes, and more reliable production of useable embryos, than natural cycle retrievals [33]. The aromatase inhibitor, letrozole, administered at a dose of 2.5–5 mg daily in combination with low-dose FSH results in a greater number of embryos from each cycle than tamoxifen alone, and a lower peak estrogen level when compared with tamoxifen alone or tamoxifen with FSH [34]. Azim and colleagues have found no increased incidence of breast cancer recurrence or decreased survival in women undergoing COS with the addition of letrozole compared with women who had no COS (mean follow-up 33 months) [35]. While these data are encouraging, additional studies with longer follow-up periods will be needed to clarify the safety and advantages of these regimens.
- In addition to concerns about the possible effect of hormonal stimulation for breast cancer patients, oncologists may question the safety of delaying cancer therapy for oocyte retrieval and IVF. In a recent study conducted at Stanford University Medical center, Madrigrano *et al*. found that the average time interval from fertility consultation (performed in 20 of 23 patients after definitive surgery but before initiation of chemotherapy) to oocyte retrieval was 33.3 days, and the entire time from consultation to initiation of chemotherapy was 46.8 days [36]. These data indicate that egg retrieval and cryopreservation can be integrated into the initial work-up of the breast cancer patient in a timely fashion. Furthermore this study underscores the importance of early intervention for fertility preservation.

Oocyte cryopreservation

- For women who are not in a position to create embryos, particularly young women who do not have a partner or a source of donor sperm, the option to cryopreserve unfertilized oocytes provides an alternative for preserving future fertility. Patients undergo a cycle of hormone stimulation using the same regimens used in traditional IVF, and oocytes are retrieved and then cyropreserved for use at a later date.

Though this technique has been available since 1986, initial results with oocyte cryopreservation and thawing were poor due to problems with intracellular ice formation and the osmotic effect on the oocyte. Only 100 live births resulting from this technique had been reported before 2004 [37]. Since then, advances have been made in oocyte cryopreservation techniques. Preservation by the ultra-fast freezing method known as vitrification, avoids ice crystal formation, and modifications in the freezing solution such as higher sucrose concentration and the addition of stabilizing substances such as proteins and anti-oxidants, have improved oocyte survival and pregnancy rates [38]. Recently, a birth rate of 5–6% per thawed oocyte has been described, with over 500 babies reportedly born using these methods [39].

Ovarian tissue cryopreservation

- A fertility preservation technique that does not require exposure to an elevated serum hormonal milieu is ovarian tissue retrieval [40]. Criteria used to identify women for this procedure are the same as for IVF. This technique may also be optimal for women who are not in a position to create embryos. Tissue from the ovarian cortex, which is rich in oocytes, is retrieved prior to the start of therapy. Once the ovarian tissue is removed, ovarian cortical tissue strips can be cryopreserved or individual follicles can be aspirated from the ovary and cyropreserved [6].
- Following the completion of cancer therapy, ovarian cortical tissue can be used for subsequent re-transplantation. Sanchez and colleagues in the Valencia program for fertility preservation report modest success with retrieval of ovarian cortex before chemotherapy, cryopreservation of the entire tissue strip, and the reimplantation of this cortical strip onto the contralateral ovarian medulla after treatment had concluded. Of the four implants performed by their group, 50% have regained ovarian function with no live births [41]. There have been three reports of live births from ovarian tissue reimplantation for women with cancer [42–44]. However, the reintroduction of tissue into cancer patients is considered suboptimal as it carries a potential risk of also reintroducing cancer cells to the patient. Additionally, certain malignancies more commonly involve the ovary, such as hematologic cancers, and thus tissue re-transplantation should be avoided in this setting. While improved cancer screening methods for ovarian tissue are on the horizon, current patient data sets are small and the risks and benefits of this technique are not well defined. At present, this procedure should be undertaken only at centers with an approved research protocol that includes some form of ovarian tissue screening for occult malignancy.
- Another option for utilizing cyropreserved ovarian tissue following cancer therapy is a still experimental procedure called in-follicle maturation (IFM). Follicle development and oocyte maturation are highly dependent on the three-dimensional architecture of the follicle and its extracellular matrix [45]. Accordingly, there has been a relative lack of successful cryopreservation of oocytes in two-dimensional culture when compared to cryopreservation of fertilized embryos. In contrast to conventional oocyte cryopreservation, the IFM procedure entails recovering intact *immature* follicles from ovarian cortex tissue, growing and maturing the entire follicle (i.e., oocyte and supporting

granulose and theca cells) *in vitro*, and then using the oocyte for IVF. Three-dimensional synthetic scaffolds, first used in the field of tissue engineering, are being used to grow individual follicles in order to maintain the intimate physiological connections between the oocytes and their surrounding support cells *in vitro* [46•]. Use of these scaffold substances for IFM has thus far been successful in animal models, resulting in the birth of live, fertile offspring and is showing promise in human tissue studies as well [47, 48].

Preimplantation genetic diagnosis

- For women with heritable breast cancers, such as BRCA1 and BRCA2 mutation carriers, the thought of having biological offspring poses additional concerns. For these patients, there is a 50% chance of having a child with a mutated BRCA gene. The technology to screen embryos for many heritable genetic mutations has been available since the early 1990s, and has been employed in over 1000 live-born infants worldwide [49]. Preimplantation genetic diagnosis (PGD) entails the aspiration of 1–2 cells from a 6 to 8 cell embryo resulting from the IVF process. The aspirated cells are then analyzed for deleterious genetic mutations in order to select for genetically intact embryos to use for implantation [50]. Despite the availability of this technology, BRCA 1/2 mutation carriers have been hesitant to consider its use. In a web-based survey of 284 American women with BRCA 1 or 2 mutations, 88% reported frequent or extreme worry about transmitting the mutation to their offspring, but only 8% indicated that they would consider PGD [51]. In 2006, the UK Human Fertilization and Embryology Authority approved use of PGD for lower penetrance, late-onset cancer susceptibility syndromes such as hereditary breast cancer. Like their American counterparts, although most British women supported the use of PGD, few said they would personally undergo the procedure [52]. This technology has been used for BRCA 1/2 mutation carriers in Israel, where the rates of genetically heritable breast cancer are higher than in other nations. Issues of acceptance, access, and equity of availability as it relates to cost currently exist for PGD, making this technique more difficult to actively incorporate into fertility preservation programs.

Third-party reproduction and adoption

- Third-party reproduction (parenthood through the use of gametes donated by a third-party or through surrogacy) is an option for breast cancer survivors who are unable or who chose not to attempt a pregnancy. When, for personal or medical reasons, use of donor eggs or surrogacy is not an option, adoption is also a possibility. Rosen conducted a study examining the potential barriers to adoption for the cancer survivor, and found that bias against adoption for these women was strongest for international adoption agencies, but existed in domestic firms [53•]. This work suggests that cancer survivors wishing to adopt should investigate the attitudes of the agency early in the process of adoption screening when it is easiest to shift agencies if necessary. Table 1 includes fertility preservation options for breast cancer patients.

Table 1. Fertility preservation options for breast cancer patients

Method	Definition	Live births
Embryo cryopreservation	Harvest of oocytes, *in vitro* fertilization (IVF), cryopreservation of embryos for implantation at a later date	>350,000 [57]
Oocyte cryopreservation	Harvesting of oocytes and cryopreservation without IVF for creation of embryos at a later date	>500 [39]
Ovarian tissue cryopreservation and transplantation	Harvesting of whole ovaries or ovarian tissue, cryopreservation, transplantation back to the donor at a later date	3 [42–44]
In-follicle maturation	Harvesting and cryopreservation of ovarian tissue, extraction of immature follicles, maturation in a three-dimensional scaffold, and IVF at a later date	None
Ovarian suppression with GnRH analogs	Administration of hormonal therapy during chemotherapy to protect ovarian tissue	Difficult to quantify
Third-party reproduction and adoption	Third-party reproduction: family building through the use of donated gametes or surrogacy. Adoption: non-biological parenting	Numerous

Conclusions

- Both the causes and treatments for infertility in young breast cancer patients must be thoroughly understood by the multidisciplinary team caring for these women in order for caregivers to be effective advocates for their patients regarding this important issue. As treatments for breast cancer improve, a large community of young survivors is forming, and oncologists must help these patients to live their cancer-free future to the fullest. The exciting field of oncofertility offers hope for young patients with cancer through a better understanding of the causes of cancer- and cancer treatment-related POF and the development and refinement of fertility preservation options. Additional recommended resources for cancer patients hoping to be parents can be found at www.youngsurvival.org, www.myoncofertility.org and www.fertilehope.org [54–56].

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The issues of discrimination and other obstacles surrounding adoption and third party reproduction for cancer patients has received little attention in the medical literature. This concise and elegant critique by Dr. Allison Rosen is an excellent starting point for clinicians to gain some knowledge and sensitivity to these important issues.

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