Fertility Preservation and Breast Cancer: A Complex Problem

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A considerable number of women with breast cancer are diagnosed during their reproductive years. In the short period of time in which newly diagnosed women will need to make decisions about surgical options and adjuvant therapy, younger women with breast cancer also face the potential impairment or complete loss of their fertility.

Introduction

With improved early detection and treatment, the majority of women diagnosed with early-stage breast cancer will survive their disease. The majority of younger women will be offered adjuvant chemotherapy, and those whose tumors express estrogen receptors (ER-positive) should receive hormonal therapy for at least 5 years. Recent data suggest a benefit of extending hormonal therapy beyond 5 years, and often chemical ovarian suppression is added in young patients. As mortality has become less of an immediate threat, minimizing short-term and permanent long-term side effects should be a central goal when choosing adjuvant regimens. In addition to the risks of leukemia and heart failure, chemotherapy-induced premature ovarian failure must be considered. The insult to the ovaries by cytotoxic agents has been linked to the patient’s age at diagnosis, the type and dose of regimen used, likely genetic determinants of the host, and lifestyle factors.

There is still uncertainty about which are the most predictive biomarkers of poor ovarian reserve and impending infertility, and how to interpret their changes during adjuvant therapy for breast cancer. Several genetic markers predicting a higher likelihood of ovarian damage from treatment with specific chemotherapeutic agents are emerging and under clinical evaluation, but large randomized studies will be needed for validation.

The two most challenging groups of patients with whom to discuss fertility preservation are probably the patients whose tumors are ER-positive, as the induction of amenorrhea has been associated with better breast cancer–related outcomes, and patients with a genetic predisposition to ovarian cancer, such as women with mutations in BRCA1/BRCA2 or with Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]) genes. In women with BRCA mutations, removal of the ovaries has been strongly associated with better breast cancer outcomes and prevention of ovarian cancer.

Little is still known about the emotional toll on patients who must navigate this very complex problem with conflicting priorities in a very short time. Access to novel technologies in fertility preservation prior to the start of chemotherapy is often not facilitated or thought feasible, because of perceived and actual risks to the patient, as well as costs and time constraints.

Care providers and patients should be informed about the risks, benefits, and likelihood of success in preserving ovarian function so they can make the best informed decision at a time that is stressful for the patient.

Fertility and natural risk factors for premature ovarian failure

Each year in the United States, more than 200,000 women are diagnosed with breast cancer,[1] of whom over 50,000 are under 50 years of age, with over 11,000 under age 40. Hence, at diagnosis an increasing number of young patients with breast cancer have not ever conceived or completed family planning.

One of the most important natural factors when considering fertility preservation is the age at breast cancer diagnosis and at the anticipated completion of adjuvant therapy. Changes in lifestyles over the last 3 decades have led to a delayed onset of childbearing, and there has been a steady increase in the number of children born to women over the age of 35. Nonetheless, the number of children born to women over age 35 is considerably lower than that in younger women. Whereas 97 children are born to 1,000 US women aged 30 to 34, this rate drops to 47 births at ages 35 to 39, to 10 at ages 40 to 44, and to 0.7 in women over 45 years of age, despite many recent advances in assisted reproductive technology (ART). ART has become an integral factor in childbearing. In 2011, an
estimated 15 in 1,000 children in the United States were reported to be born through use of ART.[2] Fertility is strongly linked to the onset of menopause. In the United States, the median age of menopause, the permanent cessation of menstruation and completion of natural fertility, is estimated to be 51 years; however, natural fertility rates decrease much earlier. A steady decrease in ovarian reserve and fertility is expected to occur after age 30, with a sharp drop after age 37.[3] Premature menopause, defined as menopause occurring under the age of 40, is seen in about 1% of women. The likelihood of premature or early menopause (before age 45) is impacted by family history, smoking, ethnicity, and socioeconomic status.[4,5] These underlying risk factors should be considered in each patient when assessing the risk of chemotherapy-induced amenorrhea and the potential for successful fertility preservation.

Risk of chemotherapy-induced amenorrhea

The rate of chemotherapy-induced amenorrhea, the commonly used surrogate for infertility after chemotherapy and hormonal therapy, has been described in several excellent reviews.[6-9] Amenorrhea rates are frequently reported as secondary endpoints in large randomized studies evaluating novel therapeutic interventions for premenopausal patients with breast cancer. The induction of amenorrhea is dependent on the agent, dose, and duration of therapy; reported rates of post-treatment amenorrhea range from 10% with newer regimens and shorter durations of therapy to close to 100% in earlier studies. In addition to the aforementioned factors, the amenorrhea incidence rate is strongly associated with advancing age. Frequently, the reported data are further confounded by short follow-up of the respective study and the considerable reversibility of the chemotherapy-induced amenorrhea.

Several reports have suggested that addition of paclitaxel and trastuzumab (Herceptin) do not add to the amenorrhea risk of doxorubicin and cyclophosphamide. Patients treated with tamoxifen in addition to adjuvant chemotherapy, on the other hand, may have a decreased chance of recovering their regular menses.[7-9]

This wide range of therapy-induced amenorrhea points to the need for well-controlled randomized studies when assessing the risk of therapy-induced amenorrhea, and the potential benefits of interventions to preserve fertility and protect against ovarian damage during adjuvant therapy. It further outlines the need for biomarkers to assess the individual ovarian reserve at time of diagnosis, to facilitate a personalized calculation of the risk imposed by the cancer therapy.

Predictors of ovarian damage and permanent therapy-induced amenorrhea

FSH and inhibin. Follicle-stimulating hormone (FSH) levels and inhibin A and B levels have been used in many studies to assess and predict therapy-induced ovarian failure.[10,11] However, the fluctuations of these markers between and within cycles render them less predictable, and often both high FSH levels and low inhibin levels after chemotherapy are reversible over time and revert to pretreatment levels when menses recover.[12-14]

Anti-Müllerian hormone. Recent studies have suggested that anti-Müllerian hormone (AMH) levels may be predictive of ovarian reserve and the response to ovarian stimulation. AMH belongs to the transforming growth factor beta (TGF-β) family and is expressed in the ovarian granulosa cell of antral follicles but not in larger developing follicles.[15,16] In contrast to FSH and inhibin levels, AMH does not fluctuate during the menstrual cycle and should not be greatly influenced by the temporary cessation of menses. Several small studies have pointed to the value of AMH as a more reliable predictive marker of permanent chemotherapy-induced amenorrhea.[17-20] Assessment of AMH levels should therefore be incorporated in future studies evaluating interventions to preserve fertility in patients undergoing chemotherapy.

Antral follicle count. In addition to laboratory studies of levels of FSH, inhibin, and AMH, sonographic assessment of antral follicle counts (AFC) have recently been found to be predictive of ovarian reserve and predictors of impending menopause.[21-24] A small study suggested that the assessment of both AMH and AFC were most reliably linked to a positive response to letrozole for ovarian stimulation and the successful embryo/oocyte preservation in patients with breast cancer.[25]

It is hoped that using this approach in addition to assessing levels of AMH, inhibin, and FSH will increase the value of any of these markers in predicting the likelihood of permanent ovarian damage induced by chemotherapy in individual patients.

Benefits of Ovarian Suppression
Several studies have shown that ovarian suppression is an effective means of adjuvant therapy. Several early trials have shown that ovarian suppression is comparable to or better than adjuvant chemotherapy with cyclophosphamide, methotrexate, and fluorouracil (CMF).[26-30] TABLE 1

The National Surgical Adjuvant Breast and Bowel Project (NSABP) B30 trial evaluated the benefits of sequential vs concurrent docetaxel. A secondary aim of this trial, which included 5,351 women, was to determine the effects of prolonged amenorrhea on outcomes. The trial included three arms (Table 1) and found that women with persistent amenorrhea had longer disease-free and overall survival.[31] Surprisingly, this trial also suggested a benefit of amenorrhea in patients with hormone receptor-negative tumors. Similarly, a 12-year, late reassessment of the International Breast Cancer Study Group Trial VIII suggested that CMF followed by goserelin (Zoladex), which resulted in more pronounced and prolonged ovarian suppression, is superior to either modality alone.[29] Several smaller trials and retrospective analyses have evaluated the benefits of adjuvant chemotherapy in women with prolonged amenorrhea vs those who had early resumption of menstruation. These findings are likely prompting the reassessment of several studies in which amenorrhea was a secondary endpoint.

Further investigation has suggested very low rates of breast cancer recurrence in young premenopausal women receiving hormonal therapy with ovarian suppression and endocrine therapy in the absence of chemotherapy. A study of 1,803 patients receiving goserelin and tamoxifen or anastrozole showed disease-free survival rates of 93% in the tamoxifen group and 92% in the anastrozole group after 48 months follow-up.[32] TABLE 2

Randomized Trials Evaluating LHRH Agonists to Preserve Ovarian Function

**Interventions for fertility preservation in women undergoing chemotherapy**

**Luteinizing hormone-releasing hormone (LHRH) agonists.** Initial reports suggested considerable benefits of LHRH agonists in protecting the ovaries from chemotherapy-induced damage. However, the data showed wide ranges of reported amenorrhea, due at least in part to the highly variable chemotherapy doses and durations, and the absence of stratification by age and treatment with hormone therapy in nonrandomized trials. Table 2 summarizes the six randomized
trials evaluating agonists of LHRH (which is also known as gonadotropin-releasing hormone [GnRH]) to preserve ovarian function. In addition, another large multi-institutional trial in women with ER-negative tumors is ongoing: the Southwest Oncology Group (SWOG) 0230 trial, also called the Prevention Of Early Menopause Study (POEMS). Three of the six trials suggest a benefit from LHRH agonists, whereas three trials do not. The differences may be due in part to the shorter follow-up in the positive Egyptian trial by Badawy et al[33] and in PROMISE-GIM6 (Prevention of Menopause Induced by Chemotherapy: A Study in Early Breast Cancer Patients–Gruppo Italiano Mammella 6),[34] in which follow-up was only 6 months and 12 months, respectively. The amenorrhea rates induced by CMF followed by 2 years of endocrine therapy in the ZIPP (Zoladex In Premenopausal Patients) trial are considerably higher than those seen in trials assessing newer regimens, which may be influenced by the high median age of the patients (45 years), with premenopausal women up to the age of 54 enrolled into the trial.[31]

In the three randomized trials with longer follow-up, the benefits of LHRH agonists were no longer seen. In OPTION (Ovarian Protection Trial In Premenopausal Breast Cancer Patients), patients on goserelin actually took longer to recover their menses, but the results should be evaluated with caution, as the final results for the entire 227 patients have not been presented. The three negative trials further differ from the positive trials. Two of the trials were conducted in ER-negative patients only, and the third trial stratified patients by ER status, thus eliminating the confounding effects of hormonal therapy with tamoxifen. Of note, all of the patients who did not resume their menses in the Community Clinical Oncology Program (CCOP) trial led by our group were on tamoxifen.[14] Furthermore, the trials without benefit from LHRH agonists showed amenorrhea rates in the control arms that were much lower than those reported by Badawy et al and Del Mastro et al.[33,34] The amenorrhea rates in the control groups of the ZORO (Zoladex Rescue of Ovarian Function), OPTION, and CCOP studies are comparable with those reported from more recent studies, if the type of regimen, duration of therapy, and age of the patient are taken into consideration. The permanent amenorrhea rates for women under the age of 40 are reported to be around 15%.[7] In the setting of low risk of developing amenorrhea, the benefits of LHRH agonists may indeed be more difficult to assess.

Unfortunately, none of the trials has pointed to reliable individual biomarkers to help predict who is at risk of developing permanent amenorrhea. It has to be further recognized that the resumption of menses does not guarantee the ability to conceive.

**Assisted reproductive technology.** The high success rate of ART should now be an integral part of the discussion about fertility preservation with women who are undergoing chemotherapy. Recent reports have suggested that fecundity with ART may be similar to natural fecundity in non-cancer patients, and an estimated 15 out of 1,000 live births involve ART. Until recently, a major hurdle in embryo cryopreservation in women with ER-positive breast cancer has been the concern over artificially creating high estrogen levels during ovarian stimulation. Furthermore, perceived time and cost constraints and low estimated success rates in ART have further limited the referral for consideration of ART in breast cancer patients.

However, recent studies have suggested that ovarian stimulation can be safely accomplished with aromatase inhibitors or tamoxifen, preventing high estradiol peaks during ovarian stimulation.[35] Using high doses of tamoxifen (60 mg/d) or letrozole (5 mg/d) with low-dose follicle-stimulating hormone resulted in sufficient numbers of mature oocytes to warrant harvest, fertilization, and embryo cryopreservation. The successful harvest of oocytes can be accomplished within one menstrual cycle and is feasible prior to initiation of chemotherapy. However, embryo cryopreservation requires that the patient have a partner at the time of harvest, or donor sperm are used. Recent advances in ART, however, now also allow the cryopreservation of oocytes not requiring a partner at the time of oocyte harvest and freezing. While the success rates of delayed in vitro fertilization (IVF) with frozen oocytes are lower compared with IVF with unfrozen oocytes,[36] this method still offers women without a partner at the time of diagnosis an option for a later pregnancy with IVF.

The initiation of ovarian stimulation and oocyte harvesting typically requires one or more menstrual cycles, therefore referral to the fertility clinic should occur as early as possible in the patient’s cycle. In most patients, chemotherapy does not start until 2 to 12 weeks after surgery. A referral to the fertility specialist and a possible intervention should be feasible. We have found that most hurdles are vastly reduced when an interdisciplinary collaboration is already in place.

**Delayed pregnancy.** Given the recent recommendation of prolonged hormonal therapy in the treatment of breast cancer, subsequent pregnancy may often be delayed for several years. Both healthcare professionals and patients should feel reassured that the delay of pregnancy may not be
detrimental when donor oocytes or frozen embryos or oocytes are used. With regard to pregnancy, only the age of the oocytes but not the age of the uterus appears to be a factor in the ability to conceive. In fact, recent data suggest that when using the non-donor oocytes, the conservative rate for live births resulting from ART is strongly linked to the age of the patient at time of harvest. A conservative estimate for live birth following IVF with non-donor oocytes in women 30 years of age and younger was 63%; it was 19% at age 42 and only 7% in women over 43 years of age. The chance of a live birth when donor oocytes are used, however, was estimated to be 60% to 80%, as age, ovarian reserve, and ovarian function are no longer limiting factors.[37] The encouraging success rates in embryo and oocyte cryopreservation allow the delay of pregnancy until the woman has completed her breast cancer therapy or can more safely interrupt hormonal therapy. The success rates of offered interventions in each fertility clinic have been published annually since 1992, by the Centers for Disease Control and Prevention (CDC) under the “The Fertility Clinic Success Rate and Certification Act (FCSRCA),” and provide a valuable referral resource to healthcare professionals and patients.[38]

**Preservation of Fertility in BRCA Mutation Carriers**

The decision to retain fertility is particularly challenging when caring for women who carry *BRCA1* or *BRCA2* mutations, in whom removal of the ovaries and fallopian tubes has been shown to significantly impact breast cancer–specific and overall survival. Several reports allude to impaired fertility in mutation carriers and the possibility for these women to undergo menopause sooner than noncarriers.[39-42] However, in a large study of 2,254 BRCA carriers and 764 noncarrier controls from the same family, no clear impact of the BRCA gene mutation on fertility was found in patients at a younger age. Little is known about whether ovarian tissue in mutation carriers is more susceptible to chemotherapy damage, and if so, by what mechanism. Given the increased risk of ovarian cancer in this population and the clearly established benefits of oophorectomy with respect to breast cancer survival, protecting against ovarian damage has to be weighed against the benefits of risk-reducing bilateral salpingo-oophorectomies. Patients often struggle with the possibility of passing on to their offspring a mutation that conveys a higher cancer risk. Recent advances in pre-implantation diagnosis make it possible to reduce the chance of passing on the mutated gene. With such options, patients may find it more desirable to protect their ovaries, and to pursue fertility preservation at a younger age prior to undergoing risk-reducing oophorectomies after completion of childbearing.[43] The complexity of fertility preservation in this patient population should prompt a timely referral to well-informed experts in the field.

**Current Practice for Patients of Childbearing Age With Breast Cancer**

A survey performed by our group in 2007 suggested that even among healthcare professionals who are medical and surgical oncologists, an in-depth discussion about fertility did not occur consistently. Although physicians discussed the risk of cancer therapy on fertility, patients were not referred to a reproductive center with expertise in cancer owing to perceived risks, cost, and time constraints.[44] We found that, at the time of diagnosis, neither patients nor healthcare professionals considered fertility a high priority, in light of more pressing concerns. However, the relevance of fertility preservation shifted at later time points, when mortality no longer appeared to be an immediate concern. Not addressing fertility issues and considering potential options to preserve fertility was associated with considerable regret. These findings were more formally explored in a larger comprehensive study evaluating patterns of pretreatment fertility counseling and referrals. Although retrospective, this study surveyed more than 1,000 patients. Loss of fertility resulted in a considerable detriment to patients’ quality of life. Counseling about fertility loss and discussion of fertility-preservation options resulted in better long-term acceptance of fertility loss.[31,45,46] The group further reported that only 5% of patients whose fertility was at risk were counseled by a reproductive endocrinologist, and even fewer patients pursued fertility preservation.

**Conclusion**

Several studies have suggested that the option to preserve fertility is a very important factor for women diagnosed with cancer during their childbearing years. Despite many recent advances, however, there is still uncertainty about how to optimally predict ovarian reserve pre- and
post-therapy, and how to choose and incorporate the most successful interventions. In nonrandomized studies and three recently reported randomized studies, the use of LHRH agonists has been proposed to protect against ovarian damage during chemotherapy. However, data from three further randomized studies have not shown a benefit from LHRH agonists when newer chemotherapy regimens with shorter duration were used, and patients were stratified for hormone receptor expression and tamoxifen use. These studies also show substantially lower amenorrhea rates, and often, upon longer follow-up, resumption of menses in over 80% of women. Adding to the complexity are recent studies reporting improved breast cancer outcomes in women receiving regimens that cause prolonged amenorrhea, and non-chemotherapy regimens with prolonged ovarian suppression have high disease-free survival rates, comparable to those seen with chemotherapy. Emerging data on the benefits of hormonal therapy beyond 5 years will have to be weighed against the natural decrease of ovarian reserve occurring in patients (with the exception of women who are very young at diagnosis) over the course of 10 years. Furthermore, the recognition of a higher likelihood of late recurrences in women with hormone receptor–positive breast cancer may render the timing of pregnancy in these women particularly challenging. In times of rapid advances in reproductive endocrinology allowing preservation of embryos and oocytes, we feel that alternative strategies should be considered in addition rather than solely relying on LHRH agonists to preserve ovarian function. All women who have not completed their family planning should be offered a comprehensive consultation involving breast surgeons, medical oncologists, and reproductive endocrinologists as early as possible in the diagnosis.

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