Fertility and Reproductive Considerations in Premenopausal Patients With Breast Cancer

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**Background:** Approximately 10% of all new breast cancer diagnoses occur in young women. Although lacking medical comorbidities, these patients often have unique issues with regard to their reproductive health that merit special consideration. As breast cancer outcomes continue to improve, quality of life for patients and their families after breast cancer treatment has come to the forefront of cancer research, particularly in the growing field of oncofertility.

**Methods:** This article reviews the literature on the singular situations and controversies faced by premenopausal breast cancer patients.

**Results:** Data on amenorrhea and the effects of modern chemotherapeutic agents on amenorrhea are limited, although the role of tamoxifen in amenorrhea is more clearly defined as increasing the rate of amenorrhea across several studies. At the forefront of studies on fertility and premenopausal breast cancer patients are investigations on fertility preservation via ovarian protection and on assisted reproductive technologies. The use of gonadotropin-releasing hormone analogs for ovarian protection remains controversial and continues to be investigated.

**Conclusions:** Early integration of assessment and counseling regarding fertility preservation is part of the multidisciplinary approach in the care of the premenopausal breast cancer patient and is key to optimizing both cancer treatment and fertility plans for the future. Because of the many ongoing biological, practical, and ethical controversies surrounding oncofertility, eligible patients should be strongly encouraged to participate in clinical trials and studies to further increase our knowledge in this growing field.
Breast cancer treatment for the premenopausal patient, as with most breast cancer patients, generally consists of a combination of surgery, chemotherapy, hormonal therapy, and radiation, as determined by the patient’s stage at presentation, specific features of the disease, and general health. Given their overall lack of comorbidities and generally more aggressive disease, a large proportion of these women receive both local and systemic therapies. Although they generally lack medical comorbidities, young breast cancer patients often have unique considerations with regard to their reproductive health that merit special consideration.

Generally local treatment of breast cancer in the form of surgery and radiation has no effect on the reproductive health of patients with breast cancer, other than the specific situation of patients who undergo treatment for breast cancer while pregnant. However, the use of chemotherapy in the premenopausal breast cancer population demands particular attention on the part of the patient and the treating physicians with regard to the short-term and long-term effects on reproduction, both during and after treatment. In addition to the issues of contraception during treatment, the long-term desires of the patient with regard to childbearing and fertility should be addressed as part of the multidisciplinary approach to comprehensive breast cancer care.

As outcomes for patients with breast cancer continue to improve, quality of life for patients and their families after breast cancer treatment has come to the forefront of cancer research, particularly in the growing field of oncofertility. This review addresses the unique situations and controversies faced by the premenopausal breast cancer patient, including infertility, fertility preservation, and pregnancy.

**Ovarian Function and Adjuvant Treatment in Women With Breast Cancer**

**Effects of Chemotherapy**

Overall, a few general underlying themes summarize the relationship of chemotherapy with amenorrhea and infertility risk. Although the exact mechanism is not well-defined, chemotherapy appears to affect ovarian reserve. It is also important to note that a return of menses is not directly representative of fertility or ovarian function. Furthermore, traditional markers of ovarian function, such as follicle-stimulating hormone (FSH), lutetinizing hormone (LH), and estradiol, are also unreliable in patients who have received chemotherapy. These factors complicate the evaluation of ovarian function after chemotherapy. Anti-Müllerian hormone and ultrasound antral follicle count may prove to be more reliable predictors of ovarian reserve after breast cancer chemotherapy.

Multiple studies have demonstrated that both age and duration of treatment are independent risk factors in the development of chemotherapy-associated menopause. Women > 40 years of age and those who have received more chemotherapy cycles, regardless of the therapy, have a higher chance of menopause. Dnistrian et al demonstrated that, within 6 to 16 months of cyclophosphamide, methotrexate, and 5-fluorouracil (CMF) chemotherapy, women < 40 years of age with breast cancer had onset of amenorrhea. This time to amenorrhea was significantly shorter (2 to 4 months) for women ≥ 40 years. In a Cochrane review of the data on amenorrhea and chemotherapy, studies from 1966 to 1994 were summarized. A majority of the studies involved patients with breast cancer who had received CMF. The review noted that 66% of the patients developed amenorrhea following chemotherapy. Of these women, the possibility of reversal of amenorrhea was noted. Once again, age was the most important factor. Although only 0% to 11% of women ≥ 40 years of age resumed regular menses, this percentage was higher for those < 40 of age (39% to 55%). The majority of those who had regained their menstrual cycle did so within 29 months, with > 50% in the first 12 months after cessation of treatment. Chemotherapy can shorten the time to the development of menopause. Within the United States, the average age of menopause is 52 years. However, the Cochrane review found the age of onset of menopause to be 38 to 46 years in patients treated with chemotherapy. Valagussa et al also reported their median age of onset of menopause as 44 years following adjuvant chemotherapy with CMF with or without anthracyclines for 12 months. After exposure to chemotherapy, the risk of menopause remains continuous and is not simply a discrete event. That is, those women who do not develop amenorrhea upfront remain at risk for early onset menopause. These findings clearly demonstrate that, for women of childbearing age, fertility options need to be addressed during the prechemotherapy consultation.

Although these studies have provided valuable information on breast cancer patients, a major limitation is their focus on older chemotherapy regimens, many of which are no longer at the forefront of cancer therapy. Data are limited regarding the effects of more clinically relevant chemotherapy regimens, such as anthracyclines and taxanes, in patients with breast cancer. For example, alkylating agents such as cyclophosphamide are quite toxic to ovarian function and reserve. These agents are the leading culprits in the development of amenorrhea in breast cancer patients. This is evidenced when anthracycline-based regimens were compared with CMF: the rates of amenorrhea for patients who had received anthracycline-based chemotherapy were lower (34%), which is associated with a lower cumulative dosing of cyclophosphamide.

The effect of adding taxanes to anthracycline-based chemotherapy in young breast cancer patients has also been evaluated. At the Weill Medical College, 45 patients with stage I-IIIA breast cancer were surveyed on their menstrual histories following chemotherapy with doxorubicin (A) and cyclophosphamide (AC) vs docetaxel (T), doxorubicin, and cyclophosphamide (TAC). Although no differences in amenorrhea rates were
found at 6 months (41.7% with AC vs 29% with TAC), there was a trend of lower rates of amenorrhea at 28 months when AC was given alone (9.1% with AC vs 35.7% with TAC).³ Ovarian reserve markers, FSH and estradiol, were also collected simultaneously in this study and were found to be unreliable as markers of amenorrhea. Investigators at Memorial Sloan-Kettering Cancer Center retrospectively reviewed the charts of 166 breast cancer patients ages ≤ 40 years who received AC followed by a taxane.¹⁵ The results, in which median patient age was 36 years and mean follow-up was at least 12 months, showed that 25 patients (15%) had long-term amenorrhea and 141 (85%) resumed their menses. Compared with historical controls, these studies suggested that the addition of a taxane does not cause significantly increased rates of amenorrhea. However, there is a trend toward amenorrhea in patients receiving taxanes as part of an anthracycline-based regimen. It is important to note that these studies are not without limitations, including small sample sizes and the intrinsic biases associated with retrospective analyses.

Further studies have suggested that taxanes do have a significant effect on amenorrhea. In a retrospective analysis of 191 breast cancer patients receiving AC followed by a taxane, the addition of a taxane to the AC resulted in increased amenorrhea (odds ratio [OR] = 1.9, 95% confidence interval [CI], 1.0-3.5; \( P = .05 \)) but did not affect the reversibility of the amenorrhea (\( P = .36 \)).¹⁶ Again, a limitation of this study was its retrospective nature. The NSABP B30 study collected prospective questionnaires on menstrual history for a subset of 708 breast cancer patients treated with AC followed by doxetaxel who participated in this portion of the trial. The duration of amenorrhea was longer for those who received that additional taxane.¹⁷ However, there was no comparative arm in the study in which participants received AC alone; thus more conclusive statements cannot be made. In a similar approach, the TAC vs 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) study evaluated node-positive breast cancer patients for improvements in survival.¹⁸ A subset of participants was evaluated for amenorrhea as defined by a lack of menses for ≥ 3 months, and TAC was associated with higher rates of amenorrhea than FAC. Since this was part of a larger manuscript, details on the data collection were not reported. Thus, a comprehensive interpretation of the data is difficult, and conclusive statements cannot be made. Based on the studies to date, it is difficult to discern whether taxanes increase amenorrhea rates due to conflicting data, potential biases, and/or suboptimal data for interpretation. Randomized prospective analyses are needed for clarification.

The 2006 American Society of Clinical Oncology (ASCO) guidelines on fertility preservation concur with our conclusions. The ASCO guidelines were set forth by a panel of experts who completed a systematic review of the literature from 1997 to 2005 to determine the impact and to survey the success of numerous methods of fertility preservation in cancer patients.¹⁹ The specific methods are discussed later in this article, but the panel acknowledged the limited human data on the effects of taxanes on fertility and found that alkylating agents such as cyclophosphamide carried the highest risk of chemotherapy-induced amenorrhea. Guidelines developed by an international panel of experts were published in 2009 following the 11th meeting of the St Gallen’s Oncology Conference. Panels from both ASCO and St Gallen recommended that conversations be initiated as early as possible to help facilitate the availability of fertility preservation options. ASCO and St Gallen’s guidelines provide clinicians with an overview and expert analysis of the literature to supply a framework on fertility preservation for application in clinical practice.

**Effects of Hormonal Therapy**

Many studies have evaluated the role of hormonal therapy on the menstrual histories of breast cancer patients. Tamoxifen is the standard-of-care adjuvant regimen for hormone-positive breast cancer in premenopausal women. A 1999 study by Goodwin et al²² evaluated 183 premenopausal women with an average age of 43.7 years who had been diagnosed with locoregional breast cancer (T1-3 N0-1 M0). Following surgical resection, 45.4% of 183 patients received CMF and 13.7% received fluorouracil, epirubicin, and cyclophosphamide (FEC). Just over 25% (47 women) received adjuvant tamoxifen. In this population, the risk of menopause increased with increasing age, chemotherapy alone (regardless of type), or tamoxifen alone. The combination of chemotherapy and tamoxifen led to a small increase in the risk of amenorrhea, which did meet statistical significance. The previously mentioned retrospective analysis of 166 patients at Memorial Sloan-Kettering Cancer Center demonstrated that, of the 82 patients who received tamoxifen after chemotherapy, 17% developed amenorrhea.¹⁵ The NSABP B30 study also included a subset analysis in which the menstrual cycles of those participants (n = 708) randomized to the AC-Taxotere arm was followed over time.¹⁷ Those participants who received tamoxifen also had an increased rate of amenorrhea (\( P = .003 \)). Therefore, unlike the data regarding the effect of taxanes on menstrual history, the role of tamoxifen in amenorrhea is more clearly defined as increasing the rate of amenorrhea across several studies. Still, due to its ability to induce ovulation and the potential of teratogenic effect on a fetus,²² those premenopausal breast cancer patients taking tamoxifen should be educated on non-hormonal forms of birth control.

**Fertility Preservation in Breast Cancer Patients**

**Ovarian Protection During Chemotherapy**

Much controversy exists over the use of gonadotropin-releasing hormone analog (GnRHa) therapy for ovarian protection in breast cancer patients undergoing chemotherapy. Several studies have tried to address the
role of GnRHa therapy in preservation of ovarian function during chemotherapy (Table 1). 4, 23-28

A randomized phase II trial conducted at our center, which included 49 young breast cancer patients, was not able to demonstrate a benefit of adding triptorelin, a GnRHa, in combination with chemotherapy to reduce chemotherapy-induced amenorrhea at 12 months. 27 Gerber et al 28 also recently reported the preliminary findings of a randomized prospective multicenter study (ZORO: Zoladex Rescue of Ovarian Function) comparing the use of the GnRHa goserelin to observation alone in young hormone-insensitive breast cancer patients receiving anthracycline-containing chemotherapy. The primary objective of this study was to evaluate ovarian function at 6 months after chemotherapy (defined as two consecutive menstrual periods within 5 to 8 months after the last dose of goserelin). This study did not show a statistically significant difference between the two groups: 70% of patients receiving goserelin had preserved ovarian function compared with 57% of patients undergoing observation alone ($P = .4$). However, an Egyptian study did demonstrate a benefit in 80 breast cancer patients randomized to receiving a GnRHa combined with adjuvant chemotherapy vs adjuvant chemotherapy alone. 4

In this prospective study, 89.6% of patients in the GnRHa arm had a return of their menstrual cycle compared with 33.3% of the control group (chemotherapy without GnRHa) at 8 months after treatment. Interestingly, this study also attempted to address the question of fertility and ovarian function, as the two do not always correlate with a return of menses. In the GnRHa arm, 69.2% of patients resumed normal ovarian activity vs 25.6% in the chemotherapy alone arm. Similar to the results noted by the Weill Medical College group, markers of ovarian function, including FSH, LH, and estradiol, are unreliable in this population of patients and should not supplant a good menstrual history.

Several ongoing phase III trials are addressing this important issue. In the United States, a large trial using goserelin was initiated in 2003 by the Southwest Oncology Group. The primary objective of this trial is to assess the ovarian failure rate at 2 years after treatment. The target completion date is 2016, with a goal of accruing 416 patients. Abroad, the Ovarian Protection Trial in Premenopausal Breast Cancer Patients (OPTION) trial led by the Anglo Celtic Cooperative Oncology Group also uses goserelin and is evaluating

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A = doxorubicin, C = cyclophosphamide, T = docetaxel, F = 5-fluorouracil, M = methotrexate, E = epirubicin, An = anthracycline-based chemotherapy, CMF = cyclophosphamide, methotrexate, and 5-fluorouracil, T = paclitaxel, G = gemcitabine, va = voluntary abortion, NR = not reported, ZORO = Zoladex Rescue of Ovarian Function.
menstruation at 12 months after treatment. This study was initiated in 2004 and plans to accrue 400 patients. Another trial using triptorelin (PROMISE) by the Gruppo Italiano Mammella completed accrual of 280 patients in 2008; the results of this study have not yet been presented.

Considering the limited data in support of the use of GnRHa for the prevention of chemotherapy-induced amenorrhea, the routine use of GnRHa for ovarian protection is not presently recommended outside the context of a clinical trial.

**Assisted Reproduction Techniques for Fertility Preservation**

Embryo and oocyte cryopreservation are the two fertility preservation options that are most widely accessible to breast cancer patients in 2009. The Society for Assisted Reproductive Technology/Centers for Disease Control data from 2006 indicated that the live birth rates from frozen embryo transfers were 33.6% in women less than 35 years of age, 29.9% in the 35 to 37 age group, 25% in the 38 to 40 age group, and 20.8% in the 41 to 42 age group.34 According to the American Society for Reproductive Medicine, oocyte cryopreservation remains experimental; however, recent pregnancy rate data after oocyte cryopreservation from some centers have approached those obtained with frozen embryo transfer31 and even fresh transfers.32 In the past decade, just under 500 live births have been reported after oocyte cryopreservation worldwide32 vs just under 5,000 live births annually in the United States alone from embryo cryopreservation.39 Whereas pregnancies from cryopreserved oocytes have proliferated in the past 3 years, it is still important to note that our experience with embryo cryopreservation is vastly greater and that embryo cryopreservation should remain the first choice. This is the best option for patients with partners who are in agreement with their wishes or for women who choose to use anonymous donor sperm to fertilize their eggs. At the same time, recent improvements in oocyte cryopreservation technology offer increased hope and expectations for many women with breast cancer for whom egg fertilization is not feasible at the time of oocyte harvest.

Cryopreservation of ovarian tissue strips has been accomplished for subsequent autotransplantation. To date, fewer than 50 women undergoing fresh or cryopreserved ovarian tissue transplantations have been reported. Since 2004, 5 healthy babies have been born after their mothers underwent ovarian tissue transplantation. The mothers were all under the age of 30 years. Both orthotopic and heterotopic (most often the antecubital fossa) sites have been utilized, but all births have occurred in mothers in whom the site was orthotopic. Follicle development usually begins 4 to 5 months after the procedure, ovarian reserve markers remain elevated, and ovarian function is transient.35 At present, transplantation seems to be the only choice for thawed, previously cryopreserved ovarian tissue.

Frozen-thawed whole ovary pieces cultured in vitro show follicle survival, but investigators have been unable to achieve full maturation. Thus, in vitro oocyte maturation from thawed ovarian pieces is not yet an option.34 Unlike ovulation induction with fertility drugs, ovarian tissue cryopreservation is not dependent on the time of the menstrual cycle and is the only option for fertility preservation in children, and it also provides a large number of oocytes. There is concern that transplanted ovarian tissue could harbor malignant cells or undergo malignant transformation. Therefore, ovarian tissue cryopreservation remains experimental and investigational.

In 2009, the realistic options for fertility preservation in reproductive-age breast cancer patients are embryo or oocyte cryopreservation. Both of these approaches utilize a modification of standard in vitro fertilization (IVF) treatment. Patients undergo ovarian stimulation with fertility drugs (superovulation) and monitoring via blood tests and transvaginal ultrasound to determine oocyte maturity. Once the eggs are mature, a transvaginal ultrasound-guided oocyte retrieval is performed under intravenous sedation. This procedure takes approximately 15 minutes. Oocytes are inseminated with sperm several hours after retrieval and cryopreserved (embryo cryopreservation) or frozen without undergoing insemination (oocyte cryopreservation). The intent is for the patient to return in several years, disease-free from breast cancer, to complete the cycle.

Superovulation typically commences on day 3 of a patient’s menstrual cycle. Oocyte retrieval generally occurs 9 to 10 days later. Thus, depending on where a patient is in the menstrual cycle, the interval from the day she decides to undergo fertility preservation treatment to the day of egg retrieval could range from 2 to 5 weeks. If the patient is in the late luteal phase and menses is anticipated within several days, it may be feasible to undergo superovulation and egg retrieval prior to lumpectomy. Fertility preservation will prolong the interval from surgery to chemotherapy, but the delay need not and should not have a detrimental effect on survival. Communication between the oncology team and the IVF program, together with an IVF program that is capable of rapidly evaluating the patient and initiating superovulation, is paramount to ensuring the timely initiation of adjuvant therapy.

Superovulation involves the use of pharmacologic doses of recombinant or highly purified FSH, leading to a period of supraphysiologic estradiol concentrations. This raises theoretical concern about the safety of fertility preservation in breast cancer patients. A multicenter Australian analysis showed a transient increase in the incidence of breast and uterine cancer within the first year after exposure to fertility drugs among patients without cancer, although the overall incidence for the entire duration of the study was not greater than expected.39 A more recent study of Danish women undergoing fertility treatment did not demonstrate a strong overall association between fertility drugs and breast cancer risk.
but detected a 1.7 rate ratio of breast cancer in nulliparous patients exposed to gonadotropins.36

Although the significance of transient estrogen elevations in breast cancer patients is unclear, superovulation protocols involving the concomitant use of the aromatase inhibitor letrozole, with gonadotropins, have been developed in an effort to minimize exposure to estradiol. Letrozole is an aromatase inhibitor with approval from the US Food and Drug Administration for initial and extended adjuvant therapy for early estrogen receptor-positive breast cancer in postmenopausal women. The drug is widely used off-label by reproductive endocrinologists for ovulation induction. As an aromatase inhibitor, letrozole inhibits the biosynthesis of estradiol from testosterone in ovarian granulosa cells. Without significant concentrations of estradiol to inhibit hypothalamic gonadotropin-releasing hormone and pituitary gonadotropins (FSH and LH) by means of classic endocrine negative feedback, pituitary FSH and LH secretion increase, resulting in follicle stimulation. The rationale for letrozole-containing superovulation protocols for breast cancer patients is demonstrated in the Figure. This was developed by Oktay et al,37 who reported a significantly lower mean peak estradiol concentration of 483.4 ± 278.9 pg/mL in 47 breast cancer patients treated with letrozole and gonadotropins, compared with a mean peak estradiol concentration of 1,464.6 ± 644.9 pg/mL in 56 age-matched controls undergoing IVF for tubal factor with gonadotropins in the absence of letrozole. Total numbers of retrieved oocytes, retrieved mature oocytes, and fertilization rates were not different between the groups.

Ovulation induction protocols using tamoxifen have also been studied for breast cancer patients. Tamoxifen is structurally similar to clomiphene. Although clomiphene is more widely used as an ovulation-inducing medication, both triphenylethylenic derivatives have similar efficacy as ovulation-inducing medications.38 Tamoxifen-based stimulation protocols yield fewer mature oocytes, fewer mature embryos, yet higher estradiol concentrations than letrozole-gonadotropin protocols, hence the current preference for letrozole-based stimulation.39

Assisted reproductive technologies also afford an opportunity for women with a history or a risk of hereditary breast or ovarian cancer and an identified mutation to undergo preimplantation genetic diagnosis (PGD) as part of their fertility preservation management. PGD is most often undertaken on embryos 72 hours after fertilization, when they are typically at the 6 to 8 cell stage. The procedure involves creating a defect in the zona pellucida, removing a single blastomere (cell), amplifying that cell’s DNA signal using polymerase chain reaction (PCR), and performing mutation analysis. PGD was initially developed to avoid transferring embryos with life-threatening genetic diseases such as cystic fibrosis or Huntington chorea. The application of PGD and the practice of embryo selection to

Figure. — Rationale for letrozole-containing superovulation protocols (based on Oktay et al37). FSH = follicle-stimulating hormone, LH = luteinizing hormone.
susceptible syndromes of variable penetrance later in life, for which effective treatments are available, have been debated among ethicists and among focus groups of patients at risk for hereditary cancers. In general, patients favor the provision of PGD for hereditary breast and ovarian cancer syndromes, such as BRCA mutations. Interestingly, even women who approved of PGD have expressed concerns about broadening its availability, writing in detail about their good quality of life, their worth to society, and the availability of effective treatments. The Human Fertilisation and Embryology Authority in the United Kingdom recently approved PGD for hereditary breast and ovarian cancer in that country.40

Integrating Fertility Counseling in Breast Cancer Patients

Even patients who do not lose their menses immediately due to chemotherapy may still experience infertility.41 In a retrospective survey of 657 women ≤ 40 years of age (mean age of 32.7 years at diagnosis) from the Young Survival Coalition,42 regardless of age or stage of cancer at time of diagnosis, most of the young women were concerned about the development of infertility. Over 70% of the participants had been diagnosed with stage II–III breast cancer. The most common factors leading to the noted concern were interest in expanding or starting a family and prior difficulty with childbearing. Over half of the women (51%) reported that their concerns about infertility were adequately addressed, and as much as 29% reported that the information received in the consultation affected their treatment decisions. This study and others demonstrated that young patients do have concerns about infertility and that by addressing these concerns, treatment plans may change. Several studies conducted by Thewes et al43–45 in Australia suggest that patients desire fertility-related information at the time of diagnosis and treatment decisions, while menopausal information is applicable and desired during and after treatment. These data support ongoing counseling regarding fertility and menopause throughout the course of treatment. As more focus is placed on prolonged survival, physicians need to incorporate this valuable discussion into their practice protocol when meeting with young breast cancer patients in consultation and continue counseling regarding fertility and menopause throughout the treatment process.

There is a limited body of research regarding fertility preservation and counseling of patients regarding reproductive options, and there are a number of salient ethical and practical considerations to take into account in these situations (Table 2). Recent surveys of cancer survivors of childbearing age suggest that approximately one-half of these patients do not have a memorable discussion of infertility as a potential side effect of cancer treatment, but that a majority of patients have questions regarding delayed childbearing and its long-term effects on quality of life.42,60–61 The issue of uninformed at-risk patients is multifactorial. Young breast cancer patients facing a new cancer diagnosis may be unprepared or uncomfortable introducing a discussion of their reproductive goals, particularly relative to their cancer diagnosis.47,52,53 Several recent surveys of reproductive-age women with cancer demonstrated a need for information regarding not only regarding fertility, but also contraception and fertility preservation.50,54 Financial concerns may also affect the flow of information, on the part of both the patient and the physician.47,55 The ultimate hurdle, however, is encouraging physicians to initiate conversations regarding fertility with patients facing cancer treatment. Lack of information on the part of the physician and/or discomfort with the topic pose significant barriers.47,48,52 Considering the worsening time constraints faced by many physicians, integration of this sensitive topic into an already overwhelming consultation may not be realistic or beneficial. The addition of a social worker or oncology nurse with special training to address these issues has been explored as a reasonable compromise in centers treating a large population of reproductive-age patients, although this is not currently a common practice.49,55,56

An expert panel composed of oncologists, obstetrician-gynecologists, andrologists, reproductive endocrinologists, health services researchers, psycho-oncologists, and bioethicists was convened by ASCO to generate practice recommendations regarding fertility preservation, which were published in 2006.19 These recommendations address fertility issues for both male and female patients as well as pediatric patients facing cancer treatment. The current ASCO recommendation is for all patients of childbearing age to have an assessment of their interest in fertility by the treating oncologist prior to initiation of therapy.19 This raises concerns regarding the integration and timing of fertility preservation techniques, particularly in breast cancer patients, as consultations for systemic treatment are generally not indicated until after surgical staging. The interval between lumpectomy and adjuvant therapy is in the 6-week range, offering an adequate time interval to accomplish a fertility preservation treatment cycle. A recent nonrandomized trial reported a surgery to chemotherapy interval of 45.1 ± 31.6 days in a group of 79 breast cancer patients who chose to undergo ovarian stimulation for fertility preservation, compared with 33.5 ± 27.3 days in 138

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<th>Table 2. — Considerations in In Vitro Fertilization (IVF) for Fertility Preservation</th>
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<td>4. Will the patient seek embryo, or oocyte, cryopreservation?</td>
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<td>5. What will become of the eggs or embryos if the patient does not survive her cancer?</td>
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breast cancer patients who decided against fertility preservation ($P < .01$).57 Another small retrospective study conducted at Stanford University of breast cancer patients undergoing ovarian stimulation suggested that patients who were counseled regarding their fertility preservation options at the time of consultation with a surgical oncologist demonstrated that integration of fertility counseling and referral could be integrated with their oncologic treatment.58 However, the mean time interval from fertility referral to initiation of therapy was over 40 days in patients referred by either a medical oncologist or a surgeon. While the question of delayed therapy is an issue of great concern to physicians and patients, its true effect on outcome is unknown. It has been reported that intervals from surgery to chemotherapy of as long as 12 weeks have no impact on survival, whereas a delay of greater than 12 weeks has an adverse effect.59 This reality of a delay in therapy should be taken into consideration when counseling patients regarding their options, and it strengthens the argument for early assessment and counseling of at-risk patients.

Undoubtedly, patients with concerns regarding their reproductive function and at risk for treatment-induced infertility merit a referral to a reproductive specialist. Breast cancer patients desirous of bearing children warrant an early referral to a reproductive endocrinologist for further discussion and counseling along with a multidisciplinary approach to integrated cancer care in order to optimize her therapeutic outcome and accomplish her long-term goals. Alternatives to fertility preservation, such as adoption or pregnancy via a surrogate carrier, are also considerations to discuss with a fertility specialist based on the patient’s particular situation and desires. The collaborating IVF program must have systems in place that allow for immediate evaluation of the patient, open communication with the oncology team, and rapid initiation of fertility preservation treatment to ensure that the interval between surgery and the initiation of chemotherapy is not delayed. Mechanisms to defray the expense of assisted reproduction, such as collaborative agreements between the IVF program and fertility preservation support groups, are of practical importance. As these processes are often investigational, patients should be encouraged to participate in available clinical trials.

**Controversies**

**Effect of Fertility Treatments on Hormone-Responsive Disease**

Fertility preservation treatments may influence progression-free survival and overall survival in breast cancer patients, either by causing a delay in the initiation of chemotherapy or by causing supra-physiologic estradiol concentrations. This is an obvious issue for young patients due to the increased risk of infertility in women of childbearing age who receive chemotherapy for their breast cancer.

As noted above, one main concern during fertility treatments is the estradiol surge, especially in breast cancer patients with hormone-responsive tumors. Investigations are underway to develop methods to attenuate this surge. In a 2003 pilot study, Oktay et al.60 performed IVF on 12 breast cancer patients utilizing tamoxifen for ovarian stimulation. Compared with a historical set of 5 natural IVF patients, an average of 2.6 embryos vs 0.6 were preserved, and survival was not affected. Letrozole, an aromatase inhibitor, has also been investigated in ovarian stimulation as it has demonstrated an ability to negate the estradiol surges.58,60,61 When comparisons were made in a head-to-head study of letrozole-IVF vs tamoxifen-IVF vs tamoxifen/FSH-IVF, letrozole was superior to tamoxifen/FSH-IVF or tamoxifen alone in number of embryos preserved.57,62 Letrozole appears to be the feasible and superior regimen for embryo cryopreservation, although more evaluation is needed. Azim et al.61 followed a nonrandomized cohort of 79 breast cancer patients who underwent superovulation and fertility preservation prior to chemotherapy and 138 breast cancer patients who did not undergo superovulation. Patients had to have stage III cancer or less to be enrolled in the trial. They were included regardless of estrogen receptor, progesterone receptor, and human epidermal growth factor receptor status. Median follow-up after surgery was 23.4 months (range, 7.5 to 63.6) in the fertility preservation group and 33.1 months (4.5 to 63.6) in the nonfertility preservation group. There were three breast cancer recurrences in the fertility preservation group (3.8%) and 11 in the nonfertility preservation group (8.1%), which was not significantly different. This study is limited by small numbers, a lack of randomization, and a variable and limited follow-up interval.

**Pregnancy After Breast Cancer**

Pregnancy after breast cancer treatment is a difficult and challenging issue for young women and physicians who are often concerned that pregnancy may influence the outcome of breast cancer. Randomized prospective trials are not feasible in this specific area, but a number of retrospective or observational studies have demonstrated that pregnancy in women with a history of breast cancer does not seem to increase the risk of breast cancer recurrences or decrease survival.13,63,64 Interestingly, some studies suggest that there may even be a beneficial effect of subsequent pregnancy on survival.64-66 However, these studies are limited by a confounding bias, the potentially “healthy mother effect” that women who become pregnant after breast cancer are likely healthier and thus less likely to develop a recurrence.67

Considering that no adverse effect of pregnancy on breast cancer outcomes has been reported, women are generally advised to delay pregnancy for at least 2 years following breast cancer treatment, after which the likelihood of breast cancer recurrence is relatively decreased. A recent study from France suggested that a
pregnancy subsequent to early breast cancer in women under 35 years of age were 77% less likely to die. An alternative for patients who fear the high estrogen/high progesterone state of pregnancy is to enlist a gestational carrier to carry their pregnancy. Endometrial preparation of a gestational carrier’s uterus is straightforward, and pregnancy rates are excellent. Because fertility preservation is an emerging field, there is only preliminary experience with pregnancy outcomes. For example, of 79 patients who chose to undergo controlled ovarian hyperstimulation and fertility preservation prior to chemotherapy, only 10 have attempted pregnancy to date. Six of these women chose to use a gestational carrier. Eight pregnancies and five deliveries resulted. One patient conceived spontaneously, demonstrating that not all patients undergoing chemotherapy will be rendered menopausal.57

Women requiring tamoxifen therapy for hormone receptor-positive disease should defer pregnancy until the completion of 5 years of therapy. However, the optimal timing of pregnancy after breast cancer treatment is not clear, and women need to make an informed decision on this issue after discussions with their treating oncologist and fertility specialist with consideration of their individual preferences and prognosis.

**Conclusions**

Ten percent of all new breast cancer diagnoses occur in young women. In 2007, 23,790 cases of in situ and invasive breast carcinomas involved women under the age of 45 years.2 Although these represent a minority of breast cancer patients, premenopausal women and their physicians face a unique set of challenges with regard to their care, and the issues of fertility and family planning have rapidly come to the forefront of cutting-edge cancer care. With the improvements in survival from breast cancer and with childbearing being increasingly deferred to later in life, the intersection of breast cancer with family planning will likely continue to be a growing phenomenon.

In the breast cancer population, infertility is generally a result of systemic therapy that affects both ovarian function and ovarian reserve. While the effects of chemotherapy and hormonal therapy are dependent on age and duration of treatment, the specific mechanisms are ill-defined. The fact that traditional markers of ovarian function, including the presence of menstrual cycles, are unreliable in this patient population complicates the clinical assessment of these treatment effects. Older studies have clearly documented the association of amenorrhea with chemotherapy. However, clinically relevant regimens, particularly those integrating taxanes, have fewer defined effects on amenorrhea and infertility. Furthermore, there is a paucity of prospective data on this subject. The addition of tamoxifen for hormone receptor-positive disease also contributes to amenorrhea. The menopausal effects of tamoxifen in premenopausal women are well-documented in both prospective and retrospective studies.

With the knowledge that chemotherapy affects fertility, multiple prospective studies exploring the use of GnRHa therapy have been conducted over the past decade in an attempt to protect ovarian function in those undergoing cytotoxic therapy. The majority of these studies have not demonstrated a significant protective effect, although they continue to be the subject of scrutiny in several ongoing prospective studies. Routine addition of GnRHa for ovarian protection is presently not indicated as part of standard systemic therapy regimens.

A preemptive approach to treatment-induced infertility has been the focus of growing interest. The integration of assisted reproductive technologies, generally in the form of IVF and embryo or oocyte cryopreservation, for breast cancer patients is the subject of much interest. Currently, cryopreservation of embryos is the recommended course of action for patients pursuing fertility preservation. Oocyte cryopreservation is still considered experimental, but use of this technology and reports of pregnancies resulting from fertilizing thawed oocytes are growing exponentially. Cryopreservation of ovarian tissue strips followed by either autotransplantation or oocyte in vitro maturation is the subject of limited studies but is for investigational use only.

An integrated, multidisciplinary approach to both cancer care and family planning is the optimal setting to maximize cancer therapeutics and reproductive interests of the premenopausal patient. Timely assessment and counseling of premenopausal patients by oncologists as well as reproductive endocrinologists are key to identify at-risk patients and to minimize delays in treatment. Education of both patients and practitioners is an ongoing challenge, and all patients of childbearing age should be considered for potential referral to a reproductive endocrinologist when they present with a cancer diagnosis. In discussions regarding fertility preservation, additional options to consider include pregnancy via a surrogate carrier or adoption, based on the patient and her situation.

Clearly, the field of cancer-related infertility and fertility preservation, dubbed oncofertility, is in its infancy, and further studies are warranted. Even in this early stage, there are a number of salient controversies particular to the breast cancer population. In addition to numerous ethical and practical considerations, the effects of hormonal manipulation on hormone receptor-positive disease, the timing of pregnancy after breast cancer treatment, and the potential delays of therapy introduced by assisted reproductive technologies are all the subjects of ongoing investigations. In addition to improving patient, physician, and provider education, enrollment in clinical trials should be encouraged for all premenopausal breast cancer patients considering their fertility options after breast cancer treatment.

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