Chapter 96
Reproductive Issues in Breast Cancer Survivors

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Breast cancer is one of the most commonly diagnosed malignancies in women of childbearing age. Approximately 10% of women diagnosed with breast cancer are younger than age 45, translating to more than 23,000 women in the United States yearly and tens of thousands more worldwide (1,2). In light of improvements in the diagnosis and treatment of breast cancer and an increasing focus on survivorship issues, combined with the sociodemographic trend of delaying childbearing, an increasing number of young breast cancer survivors are interested in future fertility. Breast cancer treatment can diminish or destroy a woman's reproductive potential owing to direct gonadal toxicity or the natural waning of fertility during the time needed to receive optimal therapy. Many young women remain premenopausal and fertile for at least some period of time after breast cancer treatment, and some are interested in interventions to preserve fertility (3). Because of the intricate relationship between breast cancer and hormones, consideration of fertility and reproductive issues in this population is complex. Reproductive factors are associated with the risk of developing breast cancer, and hormonal manipulations and medications are a mainstay of breast cancer treatment. Amenorrhea is associated with improved prognosis compared with women who continue to menstruate through chemotherapy, in the absence of tamoxifen (4–6). (See Chapter 92 on breast cancer in young women and Chapter 50 on chemoendocrine issues.) Nevertheless, for some young women with breast cancer, the threat or experience of infertility may be particularly distressing (3,7). The founder of Fertile Hope, an advocacy organization that supports fertility preservation for cancer patients, proclaimed about her cancer diagnosis, "The thought of being sterile was almost as devastating as my cancer diagnosis itself" (www.fertilehope.org). Some women are also interested in avoiding potential ill-health effects of premature menopause, including menopausal symptoms, bone thinning, cardiovascular problems, and mental health issues (3,8–10).

EFFECT OF BREAST CANCER TREATMENT ON OVARIAN FUNCTION

Fertility in young women with breast cancer may be affected by several factors. First, the time required to receive systemic breast cancer treatment can last months (e.g., conventional cytoxic chemotherapy) to years (e.g., biologic therapy, including trastuzumab or adjuvant tamoxifen). During treatment, while pregnancy is contraindicated because of the risks of teratogenicity, ovarian function and fertility are declining owing to the natural decrease in ovarian reserve with aging (Fig. 96.1). The average age of menopause in Western societies is 51 years. Adjuvant chemotherapy results in direct toxicity to the ovary, and potentially premature menopause. The degree of damage to the ovaries will determine whether amenorrhea is temporary or permanent. Chemotherapy interferes with dividing cells in the ovary, generally maturing follicles (11). Because alkylating agents, such as cyclophosphamide, are not cell-cycle specific, they may also directly kill oocytes and pregranulosa cells of primordial follicles. Evidence is mixed about whether chemotherapy given during the follicular phase of the menstrual cycle is more injurious to ovarian function (12–14). Reports of the risk of menopause, meaning a permanent loss of menses associated with an absence of residual functional oocytes, range between 10% and 90%, depending on the regimen given, the age of the patients, and the definition used for menopause. Most studies are limited by having used chemotherapy-related amenorrhea (CRA) as a surrogate for menopause and infertility. Treatment regimens vary substantially, and follow-up is heterogeneous, and usually relatively short. CRA may be temporary, especially in very young women, and older women are more likely to have permanent amenorrhea. Chronically, anovulatory women may remain fertile even if they are not having menstrual cycles, and ongoing menses are a poor surrogate for fertility, especially as women age, because of waning egg quality. Available data confirm that risk of CRA is related to increasing age and increasing cumulative dose of cytotoxic chemotherapy, in particular, alkylating agents (15). A prospective longitudinal survey of 595 women in the United States with breast cancer diagnosed at age 25 to 40 undergoing adjuvant chemotherapy confirmed that menstrual cycles were less likely to persist at 1 year among women treated with regimens containing higher cumulative doses of cyclophosphamide (i.e., cyclophosphamide, methotrexate and 5-fluorouracil [CMF] or 5-fluorouracil, doxorubicin; and cyclophosphamide [FAC] rather than doxorubicin and cyclophosphamide [AC], doxorubicin, cyclophosphamide, and paclitaxel [ACT]; or doxorubicin, cyclophosphamide, and docetaxel [ACD]) (odds ratio [OR] .37, 95% confidence interval [CI], .37–.67), although women who received CMF were more likely than those on AC, ACT, or ACD to bleed during the 1 month following chemotherapy (~50% vs. 20%, OR, 2.9, 95% CI, 1.7–5) (16) (Fig. 96.2). Rates of menstrual bleeding 6 months after completion of chemotherapy were also strongly related to patient age, with approximately 85% having ongoing menses among women age younger than 35 years, 61% in women ages 35 to 40, and less than 25% in those older than 40 (Fig. 96.3). Recent evidence suggests that the addition of the taxanes, including paclitaxel in particular, to anthracycline-based adjuvant chemotherapy confers little or no increased risk of CRA, although data are mixed (17–20). Table 96.1 details risk of CRA with common adjuvant therapy regimens by age (15).

Even among women who remain premenopausal after cytotoxic therapy, menopause may ensue sooner than would have been expected. An analysis of International Breast Cancer Study Group (IBCSG) Trials V and VI revealed that 227 women who were menstruating and disease free at 2 years after diagnosis and treatment with six to seven cycles of CMF had earlier menopause compared with controls (21). For a woman who was age 30 at the time of diagnosis, and menstruating 24 months after six cycles of CMF, there was a 37% risk of menopause only 3 years later (at age 35), and an 84% risk at age 40. Accumulating data indicate that ovarian reserve is diminished even in young women who remain premenopausal after chemotherapy for breast cancer (22–25). Hormonal treatments appear to primarily impact fertility owing to delaying childbearing, allowing natural waning of ovarian function (26).

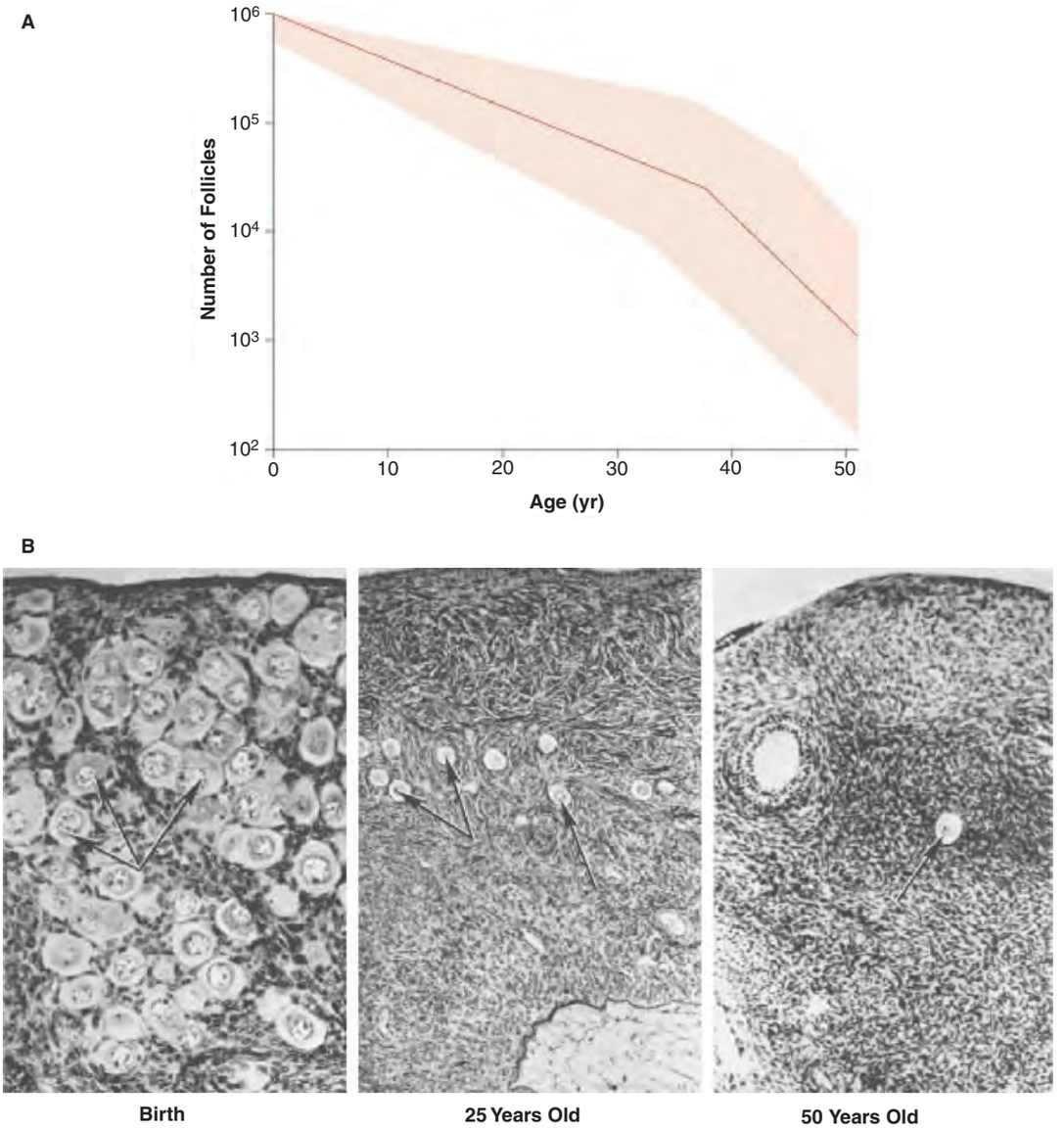

FIGURE 96.1. Natural decline in oocytes over time from birth to menopause.(Adapted from Lobo RA. Potential options for preservation of fertility in women. *N Engl J Med* 2005;353(1):64–73, with permission.) **Panel A** depicts the decline in human ovarian oocytes by age (Data from Faddy MJ, Gosden RG, Gougeon A, et al. Accelerated disappearance of ovarian follicles in mid-life: implications for foreca sting menopause. *Hum Reprod* 1992;7(10):1342–1346, with permission.) **Panel B** shows histologic specimens of oocytes (*arrows*) from birth, age 25 years, and age 50 years. (Adapted from Erickson GF . Ovarian anatomy and physiology . In: Lobo RA, Kelsey J, Marcus R, eds . *Menopause: biology and pathobiology*. San Diego: Academic Press, 2000:13–32, with permission.)

CONSIDERATIONS FOR WOMEN WHO DESIRE TO HAVE A FUTURE BIOLOGICAL CHILD

The American Society of Clinical Oncology (ASCO) has published recommendations regarding fertility preservation considerations for cancer patients (27). For women with breast cancer, strategies for fertility preservation have scarce efficacy or safety information. These limitations may hamper discussion of these issues, referrals to reproductive specialists, and the enthusiasm for patients and providers to utilize them (28–30). The first step in counseling breast cancer patients regarding their fertility is to determine the patient's desire for a future biological child (Fig. 96.4). The risk of premature menopause and infertility associated with various treatment options must be understood so that a patient can weigh the pros and cons of fertility-sparing strategies, in the risk-to-benefit analysis of her cancer treatment options. Some women may elect to forego some therapy if the incremental benefits are modest and the risk of subsequent infertility is high (3). For those who desire a future biological child and need systemic therapy which will put them at risk for premature menopause, fertility preservation strategies are available. Although studied in other cancer populations, limited enthusiasm exists in utilizing oral contraceptives through chemotherapy in young

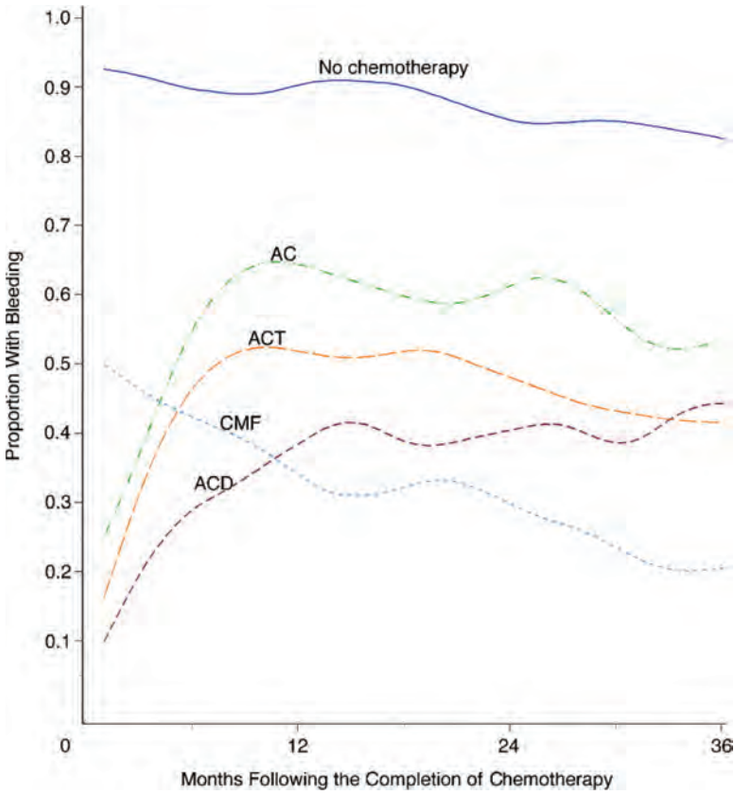

FIGURE 96.2. Menstrual bleeding by chemotherapy regimen received. (Adapted from Petrek JA, Naughton MJ, Case LD, et al. Incidence, time course, and determinants of menstrual bleeding after breast cancer treatment: a prospective study. *J Clin Oncol* 2006;24(7):1045–1051, with permission.)

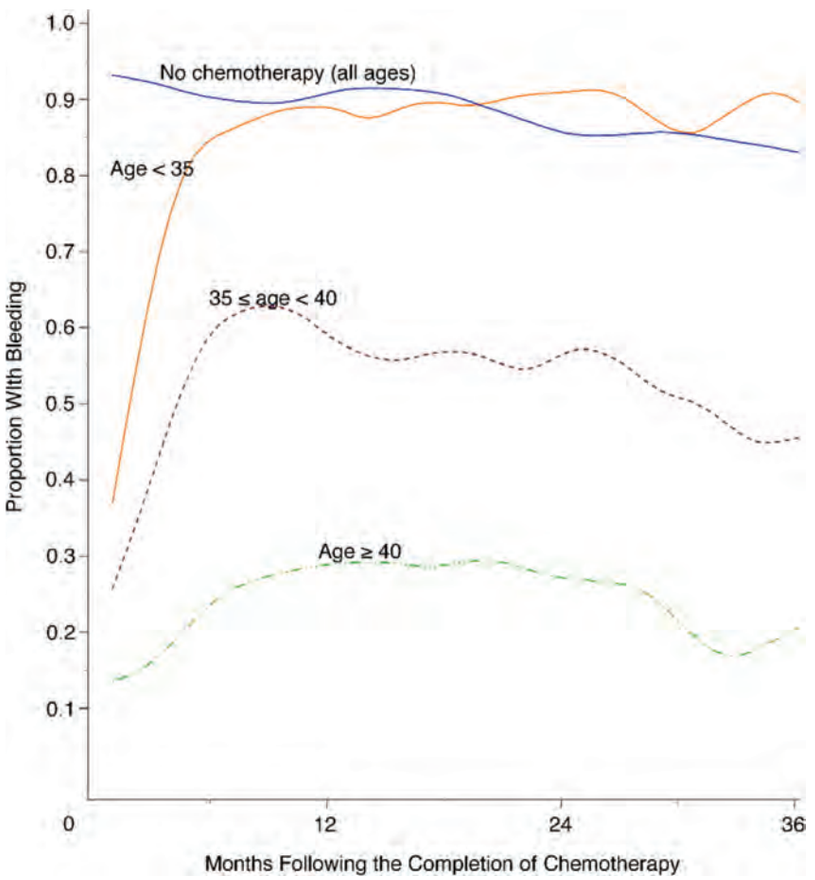

FIGURE 96.3. Menstrual bleeding by patient age at receipt of chemotherapy. (Adapted from Petrek JA, Naughton MJ, Case LD, et al. Incidence, time course, and determinants of menstrual bleeding after breast cancer treatment: a prospective study . *J Clin Oncol* 2006;24(7):1045–1051, with permission.)

Table 96.1 ESTIMATED RATES OF CHEMOTHERAPY-RELATED AMENORRHEA (CRA) WITH MODERN CHEMOTHERAPY REGIMENS BY AGE

Chemotherapy Regimen	CRA (%), Age ≤30[a]	CRA (%), Age 30–40[a]	CRA (%), Age ≥40[a]
None	~0	<5	20–25
AC × 4	~0	13	57–63
AC × 4 followed by T × 4	15		>38
AC × 4 followed by D × 4	6	12	35–50
CMF × 6	19	31–38	76–96
CAF/CEF × 6	23–47		75–89
FEC × 6	38		73
TAC × 6	51		

AC × 4, four cycles of adriamycin and cyclophosphamide (intravenously [IV]); T × 4, four cycles of paclitaxel; D × 4, four cycles of docetaxel; CMF × 6, six cycles of cyclophosphamide (oral), methotrexate, 5-fluorouracil; CAF/CEF × 6, six cycles of cyclophosphamide (oral), adriamycin or epirubicin, 5-fluorouracil; FEC × 6, six cycles of 5-fluorouracil, epirubicin, cyclophosphamide (IV); TAC × 6, six cycles of docetaxel, adriamycin, cyclophosphamide.
[a]Studies varied by inclusion of persons aged 30, 40, or 50 years in the younger or older age categories (5,15–17,26,74,75).
Adapted from Partridge AH, Ruddy KJ. Fertility and adjuvant treatment in young women with breast cancer. *Breast* 2007;16[Suppl 2]:S175–S181, with permission.

women with newly diagnosed breast cancer, given the concerns that excess hormones may worsen prognosis (31). Ovarian suppression with gonadotropin releasing-hormone (GnRH-) agonists (e.g., leuprolide acetate) is widely available and can be administered during cytotoxic chemotherapy. Several small studies have shown mixed results with regard to the efficacy of this strategy (32). For example, Fox et al. (33) reported that 23 of 24 premenopausal young patients with early-stage breast cancer given leuprolide through treatment remained premenopausal by 12 months after chemotherapy (33). However, of the 21 patient not lost to follow-up or death, at a mean of 34 months, 5 women had been pregnant (1 twice), with three of these six pregnancies requiring assisted reproduction techniques. There are ongoing clinical trials to evaluate the efficacy of this strategy (www.cancer.gov/clinicaltrials/SWOG-S0230; www.isdscotland.org/isd/1663.html).

Cryopreservation of either ovarian tissue or oocytes, the latter of which requires ovarian stimulation before treatment, is also an option where available. For both of these strategies, there has been only limited success to date and these procedures should be considered experimental. Cryopreservation of oocytes may be particularly appealing for patients who do not have a male partner and do not wish to use donor sperm. To date, efficacy has been only approximately 1.6% live births per frozen oocyte, three to four times lower than embryo cryopreservation (27,34). Ovarian tissue cryopreservation, in theory, could allow preservation of hundreds of primordial follicles (containing immature eggs) before chemotherapy without ovarian stimulation and the associated concerns about high hormone levels, and treatment delay, other than to remove the ovarian tissue. However, thus far only two live births have occurred following this technique, which suffers from substantial technical limitations (35,36). This technique is also associated with theoretical concerns of reintroduction of cancer cells in the reimplanted ovarian tissue removed. Cryopreservation of embryos following *in vitro* fertilization (IVF) is a standard procedure with a relatively high success rate in infertile women, at 15% to 30% pregnancy rate per transfer of two to three thawed embryos, depending on maternal age (www.sart.org). In women with breast cancer, there has been concern that ovarian stimulation for cryopreservation of oocytes or embryos, with the associated supraphysiologic estradiol and other hormone levels, might increase the risk of cancer recurrence, particularly in the setting of hormone receptor-positive disease. Estradiol levels during traditional stimulated IVF cycles can be greater than 2000 pg/mL, whereas levels average less than 200 pg/mL in the normal menstrual cycle.

Because natural cycle IVF (not utilizing ovarian stimulation) has much lower embryo yield compared with stimulated cycles,

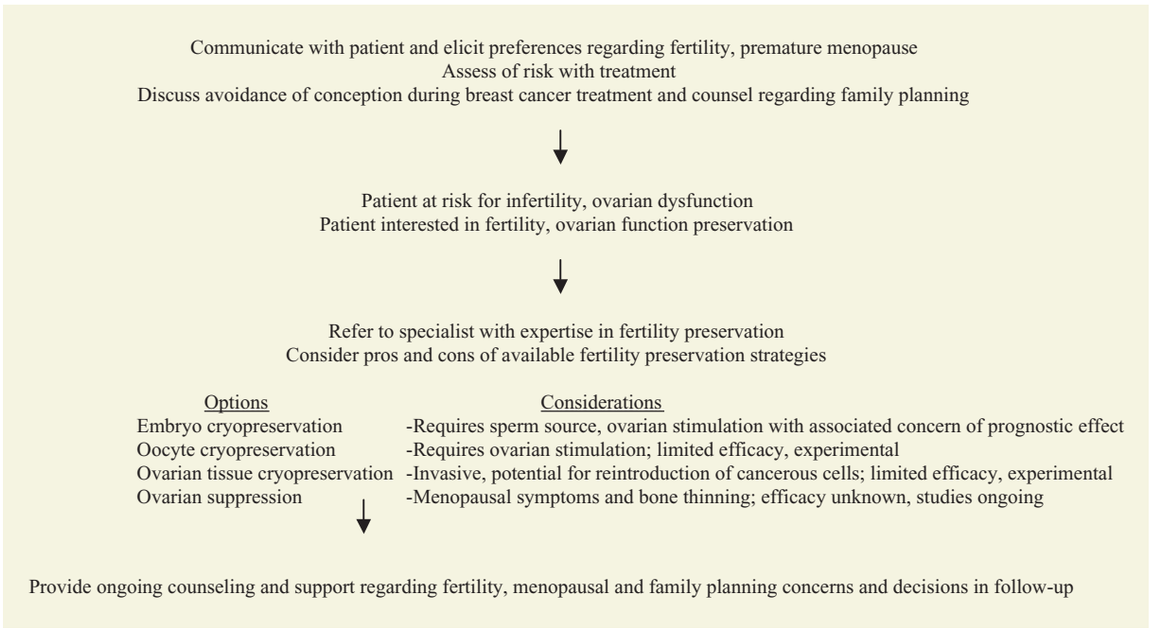

FIGURE 96.4. Management summary for premenopausal women with breast cancer regarding issues. (Adapted from Lee SJ, Schover LR, Partridge AH, et al. American Society of Clinical Oncology recommendations on fertility preservation in cancer patients. *J Clin Oncol* 2006;24(18):2917–2931, with permission.)

research evaluating alternative stimulation strategies has been conducted. Tamoxifen and letrozole have been utilized for ovarian stimulation in women with recently diagnosed early breast cancer before IVF and preliminary results are reassuring because there is a lack of clear early risks or effect on overall survival and recurrence (37–40). The 2- to 6-week period required for this procedure before beginning systemic breast cancer treatment may not be prudent in some disease settings (e.g., inflammatory breast cancer), although is reasonable without undue delays in other settings, such as in the interval between surgery and the start of chemotherapy (41).

Infertility can be devastating for some individuals and relationships, and limited research in cancer survivors suggests infertility in this population is also quite distressing (42,43). Many young women with breast cancer struggle with the competing interests of optimizing personal survival, and the powerful desire to have a future biological child (44). For some women, modifications of treatment, or intervention aimed at fertility preservation, or a combination, may be appropriate. Many other women and their loved ones choose to avoid any potential personal risk, and modify expectations regarding future biologic children, often considering alternatives such as adoption.

ASSESSMENT OF OVARIAN FUNCTION AND FERTILITY AFTER BREAST CANCER

Many survivors are interested in understanding their reproductive potential, but assessment of fertility and even menopausal status after treatment for breast cancer can be complicated and imprecise. Interruptions in menstrual cycles are not sensitive or specific for infertility. Temporary amenorrhea is common after chemotherapy, even in women who resume menstrual functioning, and hormonal treatments make the presence or absence of menses a less accurate reflection of reproductive potential. In a prospective cohort of 595 premenopausal women age 20 to 40 at diagnosis of early breast cancer, women experiencing monthly bleeding decreased from 90% to 40% following the first dose of chemotherapy (16). The rates of monthly bleeding rose to 55% over the next 15 months, but then 5 years after diagnosis slowly declined to 35%. Women who were taking tamoxifen were 15% less likely to be menstruating at 1 year, presumably because of temporary ovarian dysfunction during treatment. Follicle-stimulating hormone (FSH) level less than 20 mIU/mL, luteinizing-hormone (LH) less than 20 mIU, and estradiol (E2) more than 20 pg suggest that ovulation is still possible (45). However, even within the normal ranges of these hormones, there may be a correlation between higher levels and poorer chance of conception (46). Women with decreased ovarian reserve often have shorter menstrual cycles because of accelerated follicle development. FSH levels on the third day of menses greater than 10 mIU/mL, resulting in E2 levels greater than 75 pg/mL, cause early ovulation, which is associated with limited fertility. Inhibin levels and anti-mullerian hormone (AMH) levels may also clarify fertility status. Inhibin A is primarily secreted during the luteal phase, whereas inhibin B is primarily secreted during the follicular phase. Levels of both decrease during chemotherapy, but increase to normal range in those who eventually resume menses (47,48). AMH is produced by early-stage ovarian follicles and, therefore, reflects ovarian reserve present as reflected by the pool of remaining primordial follicles (49). Vaginal ultrasound can be used to measure antral follicle counts (AFC) on the third day of the menstrual cycle. The number of follicles measuring 3 to 10 mm or greater correlates with potential fertility (50). Hormonal manipulation can have a major impact on these values. Estradiol can be four to five times higher and FSH can be markedly suppressed on tamoxifen. Consequently, AFC while on tamoxifen may not accurately reflect ovarian reserve. AMH is produced by very early follicles and is not influenced by menstrual cycle phase, so it may be the best indicator of ovarian reserve in a woman who has been on tamoxifen, although only limited research exists to date in this area (51).

FAMILY PLANNING AND BIRTH CONTROL AFTER BREAST CANCER

Hormonal methods of contraception generally are not recommended for breast cancer survivors because of concerns about a potential effect on breast cancer outcomes, including new primary disease. Barrier methods of contraception or insertion of a nonhormonal intrauterine device (IUD) can be considered to prevent unwanted pregnancy, which can be particularly onerous for young survivors (52). Although no clear evidence indicate that ovulation induction or IVF increases the risk of breast cancer, there has been concern that IVF may increase risk of breast cancer in a person with a personal or family history of the disease (53). IVF has been conducted in cancer survivors, although response to stimulation, and subsequent embryo yield have been suboptimal (54).

SAFETY OF PREGNANCY AFTER BREAST CANCER

Concern exists that pregnancy after breast cancer may worsen prognosis, especially among women with hormone receptor-positive disease. To date, the effect of pregnancy after a diagnosis of breast cancer on relapse and survival has not been reported prospectively. Evidence from several retrospective studies on pregnancy following breast cancer has not shown a decrease in survival or an increase in recurrence; however, these studies are all limited by significant biases (55–67). Table 96.2 presents recent studies evaluating survival among breast cancer survivors who have a subsequent pregnancy compared with survivors who do not have a pregnancy after breast cancer. Although not all studies reach statistical significance, they all suggest that women who have a pregnancy after breast cancer may have lower risk of recurrence and death. In a large population-based study in western Australia, 2,539 women under 45 years of age diagnosed with breast cancer between 1982 and 2000 were evaluated for subsequent pregnancy and disease outcomes (67). In this study, 123 of the 2,539 women (5%) became pregnant after breast cancer and, of these, only 50 (41%) of these women had received chemotherapy. Consistent with previous studies, women who had a pregnancy after breast cancer were more likely to be alive in follow-up, and this effect was stronger if a woman waited at least 2 years after diagnosis to have a pregnancy (hazard ratio [HR] for death 0.48, 95% CI, 0.27–0.83), but was also present at trend level if the delay was between 6 and 24 months (HR = 0.45, 95% CI, 0.16–1.28). Although these data are reassuring, all studies are confounded by the "healthy mother" effect, that women who become pregnant after breast cancer are healthier and less likely to develop a recurrence at baseline compared with women who do not become pregnant (56). It is possible that there is a beneficial biologic effect from the high hormonal levels of pregnancy. High-dose estrogen and progestins are effective treatment for breast cancer, and an antitumor effect has been seen in *in vitro* and animal models, possibly owing to signaling via the insulin growth factor pathway (68). Ongoing prospective studies

Table 96.2 RECENT STUDIES EVALUATING SAFETY OF PREGNANCY AFTER BREAST CANCER

Study (Reference)	Breast Cancer Survivors with Subsequent Pregnancy (N)	Controls (N)	Relative Risk (95% CI) of Recurrence or Death
Sankila, 1994 (56)	91	471	0.20 (0.10–0.50)
Von Schoultz, 1995 (57)	50	2,119	0.48 (0.18–1.29)
Kroman, 1997 (55)	173	5,514	0.55 (0.28–1.06)
Valentgas, 1999 (60)	53	265	0.80 (0.30–2.30)
Gelber, 2001 (63)	94	188	0.44 (0.21–0.46)
Mueller, 2003 (65)	438	2,775	0.54 (0.41–0.71)
Blakely, 2004 (66)	47	323	0.70 (0.25–1.95)
Ives, 2007 (67)	123	2,416	0.59 (0.37–0.95)

CI, confidence interval.
Adapted from Partridge AH, Ruddy KJ. Fertility and adjuvant treatment in young women with breast cancer. *Breast* 2007;16[Suppl 2]:S175–S181, with permission.

may help to elucidate further the potential risks and benefits of pregnancy after breast cancer.

A common recommendation is for breast cancer survivors to wait at least 2 years after treatment before attempting a pregnancy, in an effort to get them beyond the period of highest risk of recurrence. However, the available data have not revealed any detriment in disease outcomes from pregnancy sooner. Given that many women with breast cancer are at risk of recurrence long beyond the first few years after diagnosis, and that fertility wanes with age, some women elect not to wait a substantial period of time to become pregnant after diagnosis. For women with hormone receptor-positive disease, 5 years of tamoxifen therapy is often recommended, during which time pregnancy is contraindicated. This approach is problematic for many women, given the decline in fertility over time and some may elect to forgo completion of a 5-year course of tamoxifen to try to become pregnant sooner rather than later.

PREGNANCY AND LACTATION AFTER BREAST CANCER

Whether a breast cancer survivor who is interested in future fertility ultimately becomes pregnant is complicated by a range of medical and psychosocial issues. Sparse data exist on fertility and pregnancy outcomes among women with a history of breast cancer. Findings from select populations of young women with breast cancer suggest that approximately 5% to 15% of young breast cancer survivors will become pregnant at least once after their diagnosis (33,67,69). No increased rate of birth defects among offspring conceived has been found. Three large studies including nearly 4,000 total offspring of childhood cancer survivors, excluding clearly hereditary cancers, revealed no statistically significant increase in cancers or malformations (70). Some *BRCA1* or *BRCA2* mutation carriers will consider preimplantation or prenatal genetic testing (71). Women who have been treated with cytotoxic agents in the past may be at increased risk of peripartum complications (e.g., cardiomyopathy owing to prior anthracycline and trastuzumab) although no data are available. Future research in this area is warranted, and women with a history of breast cancer treatment should consider receiving *high-risk* obstetric care during a pregnancy.

Breast cancer survivors who have a baby may be interested in breast-feeding (52). The degree to which local therapy has affected the normal breast anatomy will dictate the ability of that breast to produce milk. Women who have had a mastectomy can lactate from the opposite breast. Milk production may be limited by the lack of the second breast, and substantial asymmetry may result between the engorged, lactating breast and the contralateral chest wall, or reconstructed breast during the period of lactation. For women who have undergone breast-conserving therapy (BCT), resection of centrally located tumors, particularly if affecting the nipple–areolar complex, is more likely to impair lactation. Radiation therapy can cause lobular sclerosis and atrophy within breast tissue, which may also limit milk production (72). Asymmetry may be a problem in this situation as well with the treated breast less engorged. In a multicenter, retrospective review of 53 women who became pregnant after BCT, one-third had some lactation from the affected breast. Many of these women reported low milk output or the baby preferring the untreated breast, and only 25% of women were able to successfully breast-feed from the treated breast (62,73). Although it is evident that lactation is protective against breast cancer risk in both pre- and postmenopausal women, because the numbers are so small, no efforts have been made to evaluate the benefits of lactation in breast cancer survivors.

CONCLUSION

Young women with breast cancer have a strong desire to not only decrease their risk of recurrence, but to go on and live satisfying lives. This goal may entail the ability to have a biological child in the future, or to avoid premature menopause. Discussions about these issues should be tailored to each patient's preferences, taking into account the baseline risk of her disease, risk reduction from recommended therapy, as well as risk of infertility from treatment. Because of the time-sensitive nature of beginning treatment and some fertility preservation strategies, early referral to a fertility specialist is prudent for those interested (27). For some patients, a combination of fertility preservation strategies may be optimal, whereas many patients will elect to forgo any such intervention. Regardless, shared informed decision-making not only about conventional risks of treatment, but including these important issues is likely to lead to more realistic expectations, and better psychosocial outcomes for young breast cancer survivors.

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