Fertility Options in Young Breast Cancer Survivors: A Review of the Literature

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Purpose/Objectives: To describe the impact of treatment on fertility, discuss fertility-sparing options available for women with breast cancer, and explore pregnancy subsequent to breast cancer.

Data Sources: Published research, clinical articles, book chapters, and abstracts.

Data Synthesis: The risk of amenorrhea associated with alkylating agents in breast cancer survivors is well known. Fertility-sparing options before, during, and after treatment are possible with the use of assistive reproductive technology. Young breast cancer survivors are concerned about stimulating recurrence with subsequent pregnancy, health during pregnancy, and family matters.

Conclusions: Current data about the effects of treatment on amenorrhea, subsequent pregnancy after treatment, preservation of ovarian function during adjuvant therapy, and management of ovarian failure in young women with breast cancer are important to include in discussions and counseling.

Implications for Nursing: Young women deserve a thoughtful discussion about their concerns among their multidisciplinary team, including oncology nurses, oncologists, and social workers. Effects of treatment on fertility are well known. Women with fertility concerns should be referred to a reproductive endocrinology team at the time of diagnosis rather than after treatment has ended.

Key Points . . .

- ➤ Cyclophosphamide and advanced maternal age are the greatest risk factors for amenorrhea; paclitaxel with less total cyclophosphamide may reduce amenorrhea.
- ➤ New assistive reproductive technology options may help to preserve ovarian function.
- ➤ Case-control and population-based studies about survival after subsequent pregnancy indicate a better survival outcome. Survival may be related to a "healthy mother effect" or the antitumor effects of pregnancy.
- ➤ Counseling young women requires a thoughtful and multidisciplinary approach.

Goal for CE Enrollees:

To enhance nurses' knowledge about fertility and pregnancy issues for young women with breast cancer.

Objectives for CE Enrollees:

On completion of this CE, the participant will be able to

1. Identify factors that increase the risk of amenorrhea and ovarian failure in women undergoing treatment for breast cancer.
2. Outline options for preserving ovarian function in young women receiving treatment for breast cancer.
3. Describe the impact that pregnancy can have on young breast cancer survivors.

Less than 20% of women with breast cancer are premenopausal, yet the impact of cancer treatment on fertility is a major cause of distress among young breast cancer survivors (Dow, 1994; Dow, Harris, & Roy, 1994). Advanced maternal age (i.e., older than age 35) and the alkylating agent cyclophosphamide are well-known risk factors influencing fertility (Bines, Oleske, & Cobleigh, 1996; Lower, Blau, Gazder, & Tummala, 1999; Moore, 2000). Women who receive cyclophosphamide are four times more likely to experience ovarian failure than women who do not receive this agent (Meirow & Nugent, 2001). Each course of chemotherapy results in a significant loss of ovarian reserve. Even if women do not become menopausal during treatment, they may experience premature menopause and infertility after treatment ends (Oktay et al., 2003). Women who maintain fertility after chemotherapy and start a course of tamoxifen therapy also must delay pregnancy until after hormonal

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therapy is complete. Women who remain fertile after chemotherapy often are advised by clinicians to delay subsequent pregnancy for at least two years until the greatest risk of recurrence has passed. Unfortunately, women may have diminished ovarian reserve at the end of the two-year wait period.

Compared to men, women infrequently are referred for reproductive and endocrine counseling before treatment (Schover, Brey, Lichtin, Lipshultz, & Jeha, 2002). Fertility-sparing procedures with assistive reproductive technology (ART) are available for women but are considered more time-consuming compared to procedures for men because they may interfere with the start of cancer treatment. In addition, some female fertility-sparing procedures are based on hormonal treatments that are considered contraindicated in these patients. Today, newer treatments using ART enable selected breast cancer survivors to maintain fertility and have children after treatment. A discussion of ART options with their associated risks and benefits is important for young women who are concerned about fertility.

The purpose of this article is to describe the effects of cancer therapy on fertility, discuss fertility-sparing options available for women with breast cancer, and identify additional fertility concerns facing young women with breast cancer.

Effects of Cancer Therapy on Fertility

Chemotherapy

The effects of chemotherapy on fertility, specifically the alkylating agent cyclophosphamide, are well known and documented. Cyclophosphamide increases the risk of amenorrhea by damaging the small fraction of cycling ovarian follicles (Moore, 2000). Chemotherapy may act on primordial follicles through induction of apoptotic changes in pregranulosa cells leading to follicle loss (Meirow, 2000). Cyclophosphamide results in an increase in ovarian estrogen production followed by a decrease in circulating estrogen levels and a corresponding increase in luteinizing hormone and follicle-stimulating hormone levels in premenopausal women. The initial cytotoxic damage to the ovary may result in a compensatory increase in follicular recruitment, thus placing more ovarian tissue at risk for damage. The degree of amenorrhea varies but is related to the total dose of cyclophosphamide; therefore, as the cyclophosphamide dose increases, so does the risk of amenorrhea.

The combination of cyclophosphamide and doxorubicin (AC) may result in a decreased risk of amenorrhea compared with cyclophosphamide, methotrexate, and 5-fluorouracil (CMF). Premenopausal women younger than 50 who receive combination AC are less likely to experience amenorrhea compared to women receiving CMF (Bines et al., 1996). Lower et al. (1999) evaluated the prevalence and timing of menstrual abnormalities in 142 women with early-stage breast cancer receiving adjuvant methotrexate- or anthracycline-based chemotherapy; information was available for 109 women. Sixty-nine patients received methotrexate chemotherapy, 33 patients received anthracycline chemotherapy, and 7 patients received both treatments. Amenorrhea occurred in about a third of the patients during chemotherapy using the methotrexate or anthracycline regimen. Forty-five percent of the patients were amenorrheic one year after completing chemotherapy. Amenorrhea occurred primarily in women older than 35, although 28% of patients younger than 35 developed persistently abnormal menses.

Women of advanced maternal age who receive cyclophosphamide are at greatest risk of amenorrhea. As early as 1977, Koyama, Wada, Nishizawa, Iwanaga, and Aoki found that an average cumulative dose of 5.2 g cyclophosphamide resulted in amenorrhea in women in their 40s compared to a total dose of 9.3 g cyclophosphamide for women in their 30s. Bines et al. (1996) found the incidence of amenorrhea in women receiving CMF was 76% for women older than 40 compared to 40% of women 40 and younger. Goodwin, Ennis, Pritchard, Trudeau, and Hood (1999) further supported the knowledge that advanced maternal age strongly predicted chemotherapy-induced amenorrhea. They determined that the risk increased at age 35 for the majority of women older than age 45 experiencing amenorrhea after receiving six months of CMF or cytoxan, epirubicin, and 5-fluorouracil with or without paclitaxel.

Taxanes may decrease the risk of amenorrhea. Stone et al. (2000) reported a retrospective comparison of the rates of amenorrhea in 98 premenopausal women treated for early-stage breast cancer. Patients receiving AC were compared to those receiving AC and paclitaxel. The investigators found that the incidence of chemotherapy-induced amenorrhea increased with age but not with the addition of paclitaxel. More recently, Ibrahim et al. (2003) surveyed 320 patients at the start of chemotherapy who were randomized to adjuvant or neoadjuvant chemotherapy and younger than 50. Patients received either four cycles of paclitaxel-based chemotherapy followed by four cycles of 5-fluorouracil, doxorubicin, and cyclophosphamide (FAC) or eight cycles of FAC. Of the 146 returned surveys, 88 patients had complete data. They reported that menses resumed or was maintained in 53% of patients on paclitaxel-based chemotherapy compared with 31% of patients who received eight cycles of FAC. Using logistic regression analyses, the researchers determined taht patients receiving paclitaxel-based chemotherapy were 3.56 times more likely to resume menses compared with those receiving FAC.

Although women may continue to have normal menses after chemotherapy, regular menstrual cycles do not necessarily mean that the ovaries did not sustain cytotoxic damage. Rather, partial loss of primordial follicle reserve during treatment can result in premature menopause after therapy is complete (Meirow, 2000).

For patients receiving higher doses of chemotherapy as a result of bone marrow transplantation, this treatment causes permanent ovarian failure; however, Hershlag and Schuster (2002) reported four cases of pregnancy after the procedure: two patients with advanced breast cancer and two patients with Hodgkin disease. The patients with advanced breast cancer were 30 and 41 years old and became pregnant while on tamoxifen therapy.

Hormonal Therapy

Tamoxifen originally was synthesized as a contraceptive and was used as an ovarian induction agent in Europe, whereas a related compound, clomiphene, was used as a fertility agent in the United States (Oktay et al., 2003). In oncology, tamoxifen is better known as an antihormonal agent that decreases the risk of recurrence in women with estrogen receptor-positive breast cancer regardless of menopausal status, nodal status, or tumor size. Women with estrogen receptor-

positive tumors are advised to take tamoxifen 20 mg daily for at least five years after completion of chemotherapy. Even when premenopausal women do not experience premature menopause with combination therapy, they may have reduced potential for pregnancy because pregnancy is contraindicated while on tamoxifen. Thus, they must use birth control for at least five years. As a result, they may be perimenopausal or even postmenopausal at the end of tamoxifen therapy.

The aromatase inhibitors (e.g., anastrozole, letrozole) initially were used as second-line endocrine therapy for postmenopausal women with advanced breast cancer. Recent evidence shows that they are at least as effective as, if not superior to, tamoxifen as first-line endocrine therapy in postmenopausal women for at least two to three years (Baum et al., 2003). Because of their mechanism of action, aromatase inhibitors are not used with premenopausal women except in clinical trials.

Radiation Therapy

Primary breast radiation therapy has a negligible effect on the ovaries. Radiation therapy has an indirect effect on the ovaries through internal radiation scatter. The overall effect of radiation on ovarian function is relatively small compared with chemotherapy. However, women who have had radiation therapy and later become pregnant and carry their pregnancies to term will have very limited or absent lactation in the radiated breast (Dow et al., 1994).

In summary, advanced age and cyclophosphamide present the greatest risk of amenorrhea in women. Limited evidence shows that fewer cycles of cyclophosphamide combined with paclitaxel compared to eight cycles of cyclophosphamide may decrease the risk of amenorrhea. Women who maintain their fertility must wait at least two years to attempt subsequent pregnancy. The wait time of at least two years when women are on hormone ablation therapy may reduce the chance for successful pregnancy.

Fertility-Sparing Options for Women With Breast Cancer

Because the effects of chemotherapy on fertility are well known, women may seek ART to preserve fertility, ideally before treatment begins. Fertility-sparing options for women with breast cancer are divided into three areas: before, during, and after treatment.

Before Treatment

ART that has been used in women with breast cancer includes embryo cryopreservation combined with in vitro fertilization (IVF). Other ART procedures such as oocyte cryopreservation and ovarian cryopreservation and transplantation are considered experimental and neither procedure has been reported in women with breast cancer.

Embryo cryopreservation has been used for many years with comparable implantation rates similar to those using fresh embryos (Anderson, Kinniburgh, & Baird, 1999). This procedure provides a potential for women to conceive using their own oocytes if patients are expected to develop ovarian failure as a result of treatment. In this procedure, oocytes are removed, fertilized using standard IVF, cryopreserved, and stored. The procedure is recommended before chemotherapy begins to help ensure an adequate number of available oocytes. A disadvantage of this procedure is that it takes at least four weeks (one menstrual cycle) and may require delaying the start of cancer treatment. In addition, the patient must have an available partner or donor sperm.

Embryo cryopreservation after ovarian stimulation with tamoxifen and IVF has resulted in successful fertility preservation (Oktay et al., 2003). The investigators used tamoxifen to stimulate follicle growth and induce ovulation before the start of breast cancer treatment. Tamoxifen's dual action as an ovarian-stimulating agent and antihormonal agent was used to increase the number of oocytes. Twelve women with breast cancer received tamoxifen 40–60 mg for a week beginning on days 2–3 of their menstrual cycle and had IVF with either fresh embryo transfer or cryopreservation. The women were compared with a retrospective control group of five women with breast cancer having natural-cycle IVF to freeze embryos for fertility preservation. None of the women in the natural cycle IVF group received a gonadotropin-releasing hormone (GnRH) antagonist or ovarian stimulation. The investigators found that tamoxifen with IVF resulted in a higher number of mature oocytes and subsequent embryos per cycle. Two of six patients on tamoxifen with IVF became pregnant compared with two of five patients on natural-cycle IVF. One patient in the tamoxifen with IVF group delivered a set of twins. This limited but promising data suggest that tamoxifen with IVF offers a safe method of fertility sparing in women with breast cancer.

GnRH antagonists have been used to induce ovulation and IVF prior to chemotherapy or surgery. Conventional regimens using GnRH agonists are time consuming, with treatment extending from 20–30 days because these agents require pituitary downregulation before administration of gonadotropin. Treatment with a GnRH antagonist requires less time ($\overline{X} = 12$ days). GnRH antagonists are not associated with an initial gonadotropin secretion and are given during the later stages of follicular maturation to prevent luteinization and ovulation. Anderson et al. (1999) reported six case histories of women with newly diagnosed cancer having ovulation induction or IVF prior to chemotherapy or surgery using a GnRH antagonist. Three of the six women had node-negative breast cancer. The investigators started GnRH administration in the early follicular phase and added cetrorelix (i.e., a GnRH antagonist) from day 6 of treatment. After human chorionic gonadotropin administration, Anderson et al. successfully recovered oocytes that were fertilized and cryopreserved the embryos.

For women who are single and do not have a partner or sperm donor, oocyte cryopreservation has been used but is considered experimental. In this procedure, mature eggs are removed, frozen without fertilization, and stored. Oocyte cryopreservation takes about 12–14 days per cycle. This procedure has been used on a limited basis because it results in very few oocytes, and oocytes do not respond well to cryopreservation. No case reports of women with breast cancer using oocyte cryopreservation have been documented.

During Treatment

GnRH agonists have been used to induce gonadal quiescence and thereby protect ovarian function in premenopausal women during chemotherapy. GnRH agonists theoretically induce a prepubertal state that may reduce cytotoxic damage to the ovaries, but these treatments are considered experimental.

Fox, Scialla, and Moore (2001) examined the use of the GnRH agonist leuprolide during chemotherapy in 24 women

with breast cancer. The median age of the patients was 35 years (range = 23–42 years). All patients became amenorrheic by the third cycle of chemotherapy, and menses resumed in 23 of 24 patients within 12 months of completing chemotherapy. Six pregnancies were reported in five patients: Three pregnancies resulted in miscarriage, one was terminated because of Down syndrome, one resulted in live birth, and another woman was pregnant at the time of the study's publication. Three patients required fertility treatment but were unsuccessful in achieving pregnancy. The investigators concluded that although leuprolide is not associated with amenorrhea, its fertility-sparing effect is inconsistent.

After Treatment

Fertility-sparing options after treatment has ended are limited because cytotoxic damage may have occurred. Some women continue to have regular menstrual cycles, which may not result in successful pregnancy (Hensley & Reichman, 1998). However, data show that women can have successful pregnancies after breast cancer treatment (Dow, 1994; Gelber et al., 2001; Sankila, Heinavaara, & Hakulinen, 1994; Sutton, Buzdar, & Hortobagyi, 1990; Velentgas et al., 1999).

Parenting options for women who become infertile after cancer treatment include donor embryos, surrogacy, and adoption. According to Fertile Hope (2001), donor embryos allow the experience of pregnancy and birth, but the breast cancer survivor does not have any genetic relationship to the child. The major disadvantage of donor embryos is that recipients must have uterine preparation with estrogen and progesterone, making this a less viable option and contraindication for breast cancer survivors. Surrogacy and adoption alternatives are parenting options that may be considered.

Pregnancy After Breast Cancer

Breast cancer survivors who want to become pregnant often question whether pregnancy would stimulate recurrence of their disease and worry that their children may have a higher risk of birth defects or be at higher risk of developing cancer.

Effects of Subsequent Pregnancy on Recurrence

Women with breast cancer often express initial worry that subsequent pregnancy may increase their risk of disease recurrence. However, data do not show an increased risk of recurrence based on subsequent pregnancy alone. In one of the first retrospective institutional studies, White (1955) reported that 67% of patients with subsequent pregnancy survived at least five years and 58% survived 10 years compared with women with breast cancer not having subsequent pregnancy. Case-matching studies were conducted as early as 1965 to control for the influence of pregnancy occurring only in patients with good prognoses and found similar survival results. Case-control studies using newer treatment regimens were reported from 1990–1997 and showed similar survival rates (Dow et al., 1994; Gelber et al., 2001; Sutton et al., 1990).

Four large population-based studies examined the effect of pregnancy on survival in breast cancer survivors and determined that previous disease had no adverse effect on pregnancy. In a population-based cohort study of 5,725 women aged 45 or younger in Denmark, 173 women had subsequent pregnancy (Kroman, Jensen, Melbye, Wohlfahrt, & Mouridsen, 1997). Women having full-term pregnancy after treatment for breast cancer had a nonsignificant, reduced risk of death compared to women who had no full-term pregnancy. Miscarriage or induced abortions did not influence prognosis. Sankila et al. (1994) conducted a population-based matched survival study with more than 2,500 Finnish women younger than age 40, in which 91 had subsequent pregnancy. They found that the subjects in the control group had a 4.8-fold higher risk of death compared to breast cancer survivors with subsequent pregnancy. The researchers postulated a potential "healthy mother effect" of subsequent pregnancy, meaning that women who became pregnant were more likely to be free of disease than women who did not have subsequent pregnancy.

Von Schoultz, Johansson, Wilking, and Rutqvist (1995) evaluated 2,119 women with breast cancer who were younger than 50 years at diagnosis and found 50 subsequent pregnancies. They concluded that hormonal changes associated with pregnancy after breast cancer had little influence on prognosis. Velentgas et al. (1999) also observed no overall association between pregnancy after breast cancer and risk of death in 53 women who had subsequent pregnancies after treatment compared to 265 case-matched healthy controls. However, the rate of miscarriage among women who previously had breast cancer was 24% compared to 18% in the control group who never had breast cancer. The observed pregnancies ending in miscarriage were 70% higher than expected. Velentgas et al. attributed the difference to the result of an altered hormone profile after breast cancer treatment.

Gelber et al. (2001) evaluated the impact of subsequent pregnancy on prognosis. The investigators identified 108 patients with early-stage breast cancer through the International Breast Cancer Study Group; data were available for 94 subjects. Gelber et al. determined that subsequent pregnancy did not adversely affect the prognosis of early-stage breast cancer. The survival may reflect what is considered a "healthy patient" selection bias, but survival also was consistent with an antitumor effect of pregnancy. In a recent analysis by Blakely et al. (2004), the investigators found a 23% recurrence for women having subsequent pregnancy compared with 54% recurrence for women not having subsequent pregnancy.

In summary, the accumulated clinical evidence shows that women with breast cancer do not have adverse clinical outcomes with subsequent pregnancy. Some investigators postulate that healthy women with early-stage breast cancer are more likely to become pregnant and carry to full term. Infants born to mothers who have had breast cancer do not demonstrate an increased risk of low birth weight or birth defects compared with the general population.

Having Children After Breast Cancer

Very few reports have been documented about the experience of young breast cancer survivors having children after treatment. Dow (1994) reported the results of a qualitative study of 20 women who had children after treatment. A semistructured interview guide was used to identify reasons that the young women decided to become pregnant, describe their concerns about pregnancy, and determine helpful behaviors in making decisions to become pregnant. Participants

indicated that they were eager to resume their life goals that were stalled by breast cancer. For these women, having children was a high priority at the time of their diagnosis. Having children had many meanings for them: They believed that they were "cured," they were well enough to look forward to a future, and having children meant reconnecting with their peers, friends, and family. Having children was a strong stimulus to "get well" again. Young women with subsequent pregnancies believed that having children after treatment had the greatest impact on improving their quality of life. Children gave them a reason to start their day and provided a normal structure in their lives. Participants expressed concerns about the potential for disease recurrence, the need to be vigilant about cancer follow-up with breast examinations, and not having mammography during pregnancy. The participants identified helpful behaviors, including having a realistic perspective about a normal pregnancy, learning to live with and manage uncertainty about the future, having love and support from a partner, and distinguishing the difference between personal and medical decision making. Participants also cautioned that some family members expressed grave concern about the survivors' decision to become pregnant. Family members may not often agree with this decision; therefore, women contemplating subsequent pregnancy must be prepared for a somewhat less than enthusiastic family response.

Nursing Implications

Fertility and subsequent pregnancy are major quality-of-life concerns for young women with breast cancer. Because ART options are available, healthcare professionals should discuss these options, ideally before cytotoxic treatment begins. Timing of ART before chemotherapy provides the best chance of successful embryo cryopreservation, but women often are not aware of these options and have not received information to help them pursue ART. Referral to a reproductive endocrinologist who can work with the oncology team in helping women maintain fertility can be invaluable. In addition, because ART is associated with expenses that may or may not be covered by health insurance, the reproductive endocrinology team may provide additional guidance and develop realistic expectations of fertility-preserving outcomes with women. Some ART procedures are highly promising, but they have been used in small numbers of patients. Although limited information about ART is available, the Fertile Hope Web site (www.fertilehope.org) offers current and thorough patient information.

The type of chemotherapy may result in differences in amenorrhea based on a small number of studies. Nevertheless, a discussion about different chemotherapy options that may help to preserve menstrual function during treatment may be warranted.

Any woman over the age of 35 is considered of advanced maternal age with significant decline in overall fertility. When women are receiving treatment for several months and must wait at least two years after treatment before attempting pregnancy, their options for achieving pregnancy may become even more limited. Helping women to develop realistic expectations of pregnancy outcomes at an older age is an important supportive function.

Data about survival outcomes with subsequent pregnancy after treatment are very promising, as well as reports that having children after breast cancer helps to improve quality of life. Oncology nurses can offer hope when discussing fertility and pregnancy options with their young patients. In addition, developing a stronger partnership between the oncology team and the reproductive endocrinologist can improve information in the future with respect to fertility-sparing options and subsequent pregnancy after breast cancer.

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- BreastCancer.org
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