

Current Topics in Cancer Fertility

FOR ONCOLOGY NURSES



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Introduction

Advancements in cancer treatment throughout the past decades have significantly improved survival rates. Consequently, long-term physical and psychological side effects are becoming increasingly popular topics of cancer research. Impaired fertility is a long-term side effect experienced by many cancer patients treated before or during childbearing years, including survivors of gynecological and genitourinary malignancies, breast cancer, and other solid tumors and hematologic malignancies.

The actual incidence of impaired fertility associated with cancer and its treatments is not well documented. However, approximately 1 in 51 women and 1 in 71 men are expected to develop cancer by the age of 39, and more than 130,000 cancer patients—approximately 10% of the cancer population—are diagnosed in their reproductive years (American Cancer Society, 2001; Fertile Hope, 2005; Schover, 2004). For instance, approximately one fourth of all breast cancer patients are diagnosed prior to menopause, and between 10% and 20% of all breast cancer patients are of childbearing age (Parker, Tong, Bolden, & Wingo, 1997). Additionally, in the United States, 1 out of 900 persons aged 15 to 44 are survivors of childhood or adolescent cancer (American Cancer Society, 2002), the treatment of which can have lasting effects on fertility. Moreover, 12,400 children and adolescents (<1 year to 19 years of age) are diagnosed with cancer each year in the United States (National Cancer Institute SEER Program, 1995).

The majority of women diagnosed with cancer live more than 10 years after diagnosis (Bauer, 2003), and many are diagnosed at a time when fertility and family planning are a major focus in their lives (Partridge & Winer, 2005). Bauer (2003) examined the prevalence of infertility in female cancer survivors aged 18 to 50. Findings of the study demonstrated that 77% of the women had permanent menopause due to cancer treatment. Fifty percent had cessation of menses during cancer therapy, and for 78% of these women menses never returned. Early menopause is also of great concern for female survivors of childhood cancer. In studies of women treated for cancer before the age of 20, 42% of those treated with radiotherapy and chemotherapy reached menopause by the age of 31, compared to 5% of the control group (Wallace, Anderson, & Irvine, 2005). Moreover, women who undergo chemotherapy or pelvic radiation during their reproductive years have a 40% to 80% chance of infertility (Fertile Hope, 2005). Additional studies show that fertility in cancer survivors averages about 85% of that of their siblings, with male fertility impacted slightly more than female fertility by cancer treatment (American Cancer Society, 2002).

Many cancer survivors are left with significant anxiety and insufficient information about reproductive issues (Schover, Rybicki, Martin, & Bringelsen, 1999). The effect of cancer treatment on fertility is underaddressed, mostly due to the lack of information provided by healthcare professionals to cancer patients. To help bridge this information gap, this newsletter will discuss fertility options available to men and women diagnosed with cancer, with a special focus on fertility considerations for female breast cancer survivors.

Fertility Preservation Options for Women with Cancer

Marcia Leonard, RN, PNP

Women diagnosed with cancer frequently have questions regarding the effect of cancer therapy on their future reproductive potential. Cancer therapies, including chemotherapy and radiation therapy, may temporarily or permanently damage ovarian function, thereby precluding the option of biologic motherhood. Surgery involving the female reproductive organs can affect fertility in various ways, depending on the particular organ involved. This article describes the effects of cancer therapies on fertility and explores the options currently available for preservation of female fertility.

CANCER THERAPIES AND FEMALE REPRODUCTION

Surgery

Surgical procedures that remove organs critical to female reproduction,

such as radical hysterectomy, bilateral oophorectomy (i.e., the removal of both ovaries), and radical cystectomy in which the ovaries and uterus are removed, will result in permanent infertility. The removal of only a single ovary and its associated fallopian tube, however, does not significantly affect fertility and allows future pregnancy (Schilder et al., 2002). The removal of the uterus but not the ovaries leaves the possibility of biologic motherhood with the use of a surrogate gestational carrier—a woman who carries the pregnancy to term for the biologic mother (Brinsden, 2003).

Radiation and Chemotherapy

Infertility that arises following cancer treatment is the result of ovarian damage. Typically, this is marked by amenorrhea, elevated levels of follicle-stimulating hormone (FSH), and low

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TARGET AUDIENCE

This activity has been designed to meet the educational needs of oncology registered nurses.

PROGRAM OVERVIEW

Cancer and its treatments can significantly impair fertility in women and men, but many cancer patients are not aware of this devastating consequence. Fortunately, steps can be taken to preserve fertility during cancer treatment; options available or under investigation include shielding vulnerable reproductive system organs during radiation treatment, sperm banking, and sperm, oocyte, and embryo cryopreservation, among others. In this educational program nurses will learn about the impact of cancer treatments on fertility, options for preserving fertility in cancer patients, special considerations for women with breast cancer, and the importance of sharing this information with their patients.

PURPOSE

Provide education to oncology nurses on fertility risks and preservation options for cancer patients and survivors.

EDUCATIONAL OBJECTIVES

At the end of this activity, the learner will be able to:

- Identify the risk of infertility in cancer survivors of reproductive age
- Describe fertility options currently available to men and women
- Discuss fertility considerations for female breast cancer survivors

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**fertileHOPE**

fertility resources for cancer patients
www.fertilehope.org

Fertile Hope is a national nonprofit organization dedicated to providing reproductive information, support and hope to cancer patients whose medical treatments present the risk of infertility.

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Fertility Preservation Options for Women with Cancer (continued)

estrogen levels (Molina, Barton, & Loprinzi, 2005). Infertility induced by chemotherapy or radiation therapy is often referred to as ovarian failure, and can be a subset of premature ovarian failure (POF). The development of ovarian failure following chemotherapy or radiation therapy is dependent on many factors, including patient age at the time of treatment, the particular chemotherapy agent(s) used, the location or "treatment port" of radiation, and the total dose and duration of chemotherapy and/or radiation therapy.

Chemotherapy is the broad term used to describe cancer treatment with any one or more of many different drugs. Only some chemotherapeutic agents are known to result in infertility. Not surprisingly, higher doses of the harmful agent are more likely to result in toxic effects. Furthermore, combining different chemotherapy agents that may induce infertility individually can potentiate toxicity at a lower total dose. The class of drugs known as alkylating agents has been most frequently implicated in reproductive system compromise. Table 1 lists the chemotherapy agents known to affect female fertility (Chabner & Longo, 2005).

Table 1. Chemotherapy Agents Associated with Fertility Impairment

- Busulfan
- Carmustine
- Chlorambucil
- Cisplatin
- Cyclophosphamide
- Lomustine
- Melphalan
- Nitrogen mustard
- Procarbazine
- Temozolomide
- Thiopeta
- Vinblastine

Radiation therapy delivered near the ovaries may result in permanent infertility. Radiation to the pelvis, abdomen, or spine often includes the ovaries and uterus within the treatment port. Damage to the uterus from radiation therapy can lead to increased rates of miscarriage, premature labor, and low birth weight infants (Critchley, Bath, & Wallace, 2002). Total-body irradiation, which is sometimes used in preparation for a bone marrow transplant, always affects the ovaries. In contrast, radiation administered to areas above or well below the pelvis has no effect on ovarian function. Similar to chemotherapy, sterilizing effects of radiation treatment are dependent on dose, the fractionalization schedule, and patient age at the time of treatment. Even with low doses of radiation, women over 40 years of age at the time of treatment may have permanent ovarian failure (Wallace, Thomson, & Kelsey, 2003). Significantly higher doses are needed to induce ovarian failure in younger women and girls. However, 37 of 38 young girls treated for an intra-abdominal tumor with moderate doses of abdominal external radiotherapy developed ovarian failure (Wallace, Shalet, Crowne, Morris-Jones, & Gattamaneni, 1989). Specifically, 71% exhibited primary amenorrhea and the remainder underwent POF at a median age of 23.5 years.

Previously, it was believed that prepuberty girls are resistant to the damage of chemotherapy and radiation therapy, because progression to puberty with the establishment of monthly

cycles and hormone levels often occurs normally following cancer treatment. However, studies of longer duration and follow-ups indicate that prepubertal ovaries are as sensitive to the toxic effects of chemotherapy and radiation therapy as the ovaries of older women and suffer damage and depletion of healthy oocytes (i.e., eggs; Wallace et al., 2005). The apparent difference in toxicity is attributed to the fact that younger ovaries have significantly larger pools of oocytes. Therefore, a similar number of oocytes may be damaged with each course of chemotherapy regardless of patient age, but the larger reserve of available oocytes in younger individuals delays the onset of ovarian failure until a later time. For example, early onset menopause has been described in women treated with chemotherapy for leukemia during childhood (Byrne, 1999).

OVARIAN PHYSIOLOGY

Women are born with their entire lifetime supply of oocytes, numbering approximately 1 million and experience a continuous decline in the total number throughout their lives. By the time a girl enters puberty, only about 25% of her total oocyte pool remains—approximately 300,000 (Gosden, 1995). Most women begin to exhibit a significant decrease in fertility around the age of 37. At menopause, which occurs at an average age of 51 years, virtually no oocytes remain.

The vast majority of oocytes within each ovary are immature and are stored within small cysts called follicles. Oocytes must undergo growth and maturation to become functional. Throughout a woman's lifetime, an excessive number of follicles and oocytes are recruited to begin the growth and maturation process. The large majority, however, do not reach full maturity; most undergo spontaneous involution and disappear in a process called atresia (i.e., degeneration). Only about 300 to 500 oocytes will reach maturity during a woman's lifetime (University of Michigan, 2005).

Maturation of oocytes within the follicle typically lasts about 14 days and can be divided into two distinct periods. During the initial period many oocytes, perhaps thousands, begin to develop and grow. The second phase of development is marked by gonadal hormone stimulation and selection of one dominant follicle. The oocyte within the dominant follicle grows into a fully mature state, relying on hormones for growth and stimulation, and becomes capable of ovulation and fertilization. The remaining follicles that began development undergo atresia. When the oocyte within the dominant follicle is close to maturity the follicle bursts and releases the oocyte, which then travels through the fallopian tube toward the uterus. The oocyte is capable of being fertilized for a short period—about 48 hours. If the oocyte is not fertilized during this time it will die, and in approximately 1 week a new cycle of oocyte maturation will begin (University of Michigan, 2005).

The unique and remarkable characteristics of the human oocyte have made fertility preservation for women with cancer a daunting task. The oocyte is the largest cell in the human body and contains a significant amount of water, which makes oocytes difficult to cryopreserve. The inability to generate new oocytes, the need for oocytes to grow and mature over 14 days to become fully functional, and the production of only a single mature oocyte per month are all barriers to cryopreserving female gametes. Recent advances in reproductive medicine make fertility preservation a possibility for many women diagnosed with can-

cer. Attempts at preserving fertility for women about to undergo cancer therapy have been aimed at either protecting the ovary from the damaging effects of chemotherapy or cryopreserving ovarian material for later use.

OVARIAN PROTECTION

Efforts to decrease the overall morbidity associated with cancer therapy include the use of treatment regimens that use less toxic agents, lower doses of agents with known toxicity, and lower doses or elimination of radiation therapy. External lead shields provide some protection to the ovaries from radiation and should be employed if the shielding does not compromise the antineoplastic effects of radiation treatment. Oophoropexy, also referred to as ovarian transposition, moves the ovary from the path of the radiation therapy beam into a protected area in the abdomen. Surgical transposition of the ovaries before radiotherapy can reduce the risk of POF and infertility, as evidenced by the persistence of premenopausal gonadotropin levels following this procedure (Husseinzadeh, Nahhas, Velkley, Whitney, & Mortel, 1984). Williams, Littell, and Mendenhall (2000) found that laparoscopic oophoropexy prior to pelvic radiation is an effective method of preserving ovarian function in patients with Hodgkin's disease.

Drugs that alter the function of the ovary, such as oral contraceptive pills (OCPs) and gonadotropin-releasing hormone (GnRH) analogues, have been tested as potentially useful agents in preventing ovarian damage. The notion that ovarian function could be preserved while in a quiescent state, thus rendering the ovaries less susceptible to the damage of chemotherapy, is attractive. OCPs were initially thought to provide such pharmacologic protection. They exert their effect by inhibiting the development and maturation of the monthly dominant follicle, thereby preventing the development of a mature oocyte capable of being fertilized. However, OCPs do not affect the early development of the hundreds of other follicles that begin the maturation process; these follicles, therefore, remain susceptible to damage from chemotherapy.

Another class of drugs that affects ovarian function is the GnRH analogues, such as leuprolide and goserelin. These drugs inhibit the release of anterior pituitary hormones (e.g., FSH and luteinizing hormone) that stimulate follicle maturation and thereby return the ovary to a condition similar to the immature prepubertal state (Blumenfeld, Avivi, Ritter, & Rowe, 1999). Animal studies have shown direct ovarian protection and, therefore, a potential benefit of GnRH analogues (Meirow, Assad, Dor, & Rabinovici, 2004). Human ovarian protection with GnRH analogues remains an area of active debate and research because results of studies using GnRH analogues in females undergoing cancer treatment have thus far produced inconsistent results. Although some reports indicate a protective benefit from these agents (Somers, Marder, Christman, Ognenovski, & McCune, 2005), many others have been unable to show an advantage (Holzer & Tan, 2005; Revel & Laufer, 2002). At this time, a large-scale, randomized, prospective study using GnRH analogues is underway and should help clarify the benefit of these agents (National Institutes of Health, 2005).

CRYOPRESERVATION

Three very different practices are used in attempts to preserve the option of biologic motherhood for women with cancer who are at risk of developing infertility. They include: (1) embryo cryopreservation; (2) unfertilized oocyte cryopreservation; and

(3) ovarian tissue (i.e., immature or primordial oocyte) cryopreservation.

Embryo Cryopreservation

Embryos are fertilized oocytes that have begun initial cell divisions. The fertilized oocyte or embryo tolerates the freezing and thawing process extremely well. First performed successfully in 1984, cryopreservation of embryos has led to the birth of thousands of babies. Embryos for cryopreservation are produced in the laboratory as part of in vitro fertilization (IVF). The IVF cycle begins with exogenous hormonal stimulation of the ovary so that many oocytes, rather than the typical single oocyte, are coaxed to maturity. These mature oocytes are then removed from the ovary via transvaginal ultrasound-guided needle aspiration and placed in a petri dish, to which sperm is added. If fertilization takes place, the new cells are called an embryo. Women with cancer can then cryopreserve and store the embryos for future attempts at pregnancy when cancer therapy is completed. Another option for cancer patients is the transfer of the embryos to the uterus of a surrogate if the health of the patient precludes pregnancy. With this method, the surrogate will carry the infant to term; however, the infant has no biological relationship to the carrier.

Before considering embryo cryopreservation, a reproductive endocrinologist (a subspecialist in obstetrics and gynecology) should ensure that the cancer patient is otherwise healthy and able to tolerate high doses of hormonal stimulation. The gonadotropins used to stimulate follicular development result in extremely high levels of estrogen in the body. Some cancers, most notably breast and uterine cancer, may be sensitive to estrogen. Options for women with estrogen-sensitive tumors are described in *Fertility Considerations for Women with Breast Cancer* on page 4.

Embryo cryopreservation requires several weeks to complete, which could delay the onset of cancer treatment. In addition, a male partner is needed as a source of sperm to fertilize the oocytes. Both male and female partners share ownership of the resulting embryo, so disposition of the embryos created in the event of divorce or termination of the relationship should be discussed. Donor sperm may be used if the patient does not have a male partner; however, this may be less desirable, especially if a partner later enters the patient's life. The creation of embryos and their storage may present ethical and moral concerns to patients, and consideration of the fate of the embryos, especially if the patient succumbs to cancer, should be discussed before proceeding. Finally, the procedure may cost in excess of \$10,000 and often is not covered by third party payers, although financial assistance programs such as Fertile Hope's Sharing Hope program may lower some costs.

Success rates for IVF are difficult to estimate. Rates vary significantly and depend on the age of the woman as well as other factors, such as the IVF facility itself. Frozen embryos have a slightly lower survival and implantation rate than fresh embryos. In general, about 80% of frozen embryos survive with a live birth occurring approximately 30% of the time (Aytoz et al., 1999).

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The Impact of Cancer on Men's Fertility

Leslie R. Schover, PhD

FERTILITY AT CANCER DIAGNOSIS

Before discussing the effects of cancer treatment on male fertility, an understanding that the malignancy itself may be associated with impaired male fertility even prior to cancer treatment is critical. Testicular cancer is the most common malignancy in men aged 15 to 40, with about 8,000 new cases each year in the United States (Garner, Turner, Ghadirian, & Krewski, 2005). It is more common in men who have cryptorchidism (i.e., undescended testes), a condition that is also related to infertility. Additionally, many men diagnosed with testicular cancer have tissue abnormalities and reduced sperm production in the contralateral testis, even when it appears normal (Hoei-Hansen, Holm, Rajpert-De Meyts, & Skakkebaek, 2003). Bilateral testicular cancer is present in less than 1% of newly diagnosed men, and less than 1.9% may develop a second, invasive cancer in their remaining testicle within the 15 years following their initial diagnosis (Fossa, Chen, et al., 2005). A Danish registry study found significantly lower fertility in a cohort of 3,530 men born between 1945 and 1980 who developed testicular cancer compared to all other Danish men born in the same era (Jacobsen et al., 2000). Fertility was significantly reduced in the 2 years leading up to the cancer diagnosis and in men with nonseminomatous tumors (i.e., tumors arising from sperm cell precursors). In 3,847 men in an American infertility clinic who had abnormal semen analyses (defined as semen with low sperm concentrations and with defects in sperm morphology and motility), the rate of testicular cancer was 20 times higher than expected, reinforcing the need for infertility specialists to be watchful for this cancer (Raman, Nobert, & Goldstein, 2005).

In addition to testicular cancer, other malignancies that may occur in teens and young men include non-Hodgkin's lymphoma, Hodgkin's disease, leukemia, sarcomas, melanoma, colorectal cancer, and central nervous system tumors (Pearce, Parker, Windebank, Cotterill, & Craft, 2005; Wu et al., 2005). In Hodgkin's disease, up to 70% of male patients are found to have defects in semen quality at the time of diagnosis (Wallace, et al., 2005). In general, young men diagnosed with cancer are more likely to have reduced sperm counts and motility, perhaps due to recent fevers, anesthesia for diagnostic procedures, or other tumor-related factors (Chung et al., 2004). The semen quality of young teens, older teens, and men in their early 20's is equally affected by these factors (Wallace et al., 2005). Moreover, the sperm of men recently diagnosed with cancer also show more DNA damage than the sperm of healthy controls (Kobayashi et al., 2001; O'Donovan, 2005). Tests for DNA damage in sperm measure strand breakage or the condensation of genetic material in the nucleus. These abnormalities are associated with poor fertilization rates in natural and assisted conception (Morris, 2002).

FERTILITY AFTER CANCER TREATMENT

A number of cancer treatments damage male fertility either temporarily or permanently. For instance, surgery for pelvic or genital cancers, such as bilateral orchiectomy for testicular cancer or advanced prostate cancer, may remove a critical portion of the male reproductive system. Although many people think of men with prostate cancer as beyond reproductive age, the average age of diagnosis has decreased

due to prostate-specific antigen screening; therefore, some men are still interested in having children at the time they are diagnosed with prostate cancer (Varenhorst et al., 2005). Radical surgery for prostate or bladder cancer removes the prostate and seminal vesicles, eliminating the production of semen. Retroperitoneal lymphadenectomy performed to diagnose the extent of testicular cancer can impair fertility by causing retrograde ejaculation, but nerve-sparing surgical techniques can usually prevent this complication. However, nerves are often damaged when similar surgery is performed to remove residual disease after chemotherapy (Saxman, 2005). Surgery for colorectal cancer may cause similar impairment (Havenga, Maas, DeRuiter, Welvaart, & Trimbos, 2000).

Chemotherapy drugs and radiation therapy directed near the testes can also impair male fertility (Agarwal & Allamaneni, 2005; Howell & Shalet, 2005). Alkylating chemotherapy drugs, including platinum agents (Saxman, 2005), are the most destructive to spermatogenesis. The higher the chemotherapy agent dose, the greater the chance that all the spermatogonia (i.e., stem cells that produce maturing sperm cells) will be destroyed, causing permanent azoospermia (i.e., complete absence of sperm cells in the semen). Although some chemotherapy regimens, such as ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) for Hodgkin's disease, have been designed in an attempt to replace other highly gonadotoxic regimens and reduce the rates of permanent azoospermia, recurrent or advanced disease may necessitate treatment with a more toxic regimen (Grigg, 2004).

The damage to male gonads caused by radiation therapy can be permanent and depends on the total dose, fractionation schedule, and field of radiation. The higher the dose of radiation to which the testes are exposed, the greater the damage to spermatogenesis, but even doses as low as 0.1 to 1.2 Gy may impair spermatogenesis. Men receiving total-body irradiation prior to a bone marrow transplant commonly experience permanent azoospermia (Howell & Shalet, 2005). Therefore, patients receiving total-body irradiation are considered at high risk (>80%) for impaired fertility (Wallace et al., 2005). Testicular radiation in prepubertal boys with leukemia is also quite destructive to fertility and permanent azoospermia is an invariable consequence when testes are exposed to radiation doses of 24 Gy (Brougham & Wallace, 2005; Thomson et al., 2002). Recently, however, good recovery of spermatogenesis has been reported in men treated with brachytherapy for prostate cancer (Grocera, Mauzeri, & Zietman, 2005; Mydlo & Lebed, 2004).

Cancer survivors, as a group, tend to have decreased sperm counts and motility after chemotherapy or pelvic irradiation (Bahadur et al., 2005; Howell & Shalet, 2005). However, the degree of damage to sperm counts and motility that may occur even before cancer treatment does not accurately predict recovery of fertility after cancer treatment. For instance, men with testicular cancer have the lowest sperm concentrations (i.e., sperm count per milliliter of semen) prior to treatment, but are most likely to have some sperm cells in their semen after treatment (Bahadur et al., 2005). However, men with the lowest sperm counts after cancer have the longest times to fertility recovery. Nonetheless, in a recent study of 42 men with azoospermia at cancer diagnosis who were followed for a

median of 9 years, 12 of 17 who wanted to father a child achieved that goal (Ragni et al., 2005).

Sperm DNA damage may also occur as a result of cancer treatment (Morris, 2002; O'Donovan, 2005), although DNA repair can eventually occur. Most DNA defects are found in sperm during the first weeks after cessation of cancer treatment; abnormalities typically diminish over the next 2 years (Wyrobek, Schmid, & Marchetti, 2005). For this reason, sperm banking is not recommended once a man has been exposed to chemotherapy or pelvic radiotherapy, and most oncologists suggest waiting 6 to 12 months after cancer treatment to attempt conception (Morris, 2002; Wyrobek et al., 2005). In a clinical study comparing 33 long-term survivors of childhood cancer to 66 healthy controls, no excess DNA abnormalities were found in the sperm of cancer survivors (Thomson et al., 2002). However, 30% of the cancer survivors were azoospermic and only 33% had normal semen quality.

HEALTH OF OFFSPRING

In animal studies, sperm with DNA damage is associated with birth defects or unusual cancer rates in offspring (Morris, 2002). However, no excess rate of birth defects has been observed in children conceived during or after the father's cancer treatment (Fossa, Magelssen, et al., 2005; Meistrich & Byrne, 2002). In a study of more than 4,000 adult male survivors of childhood cancer, significantly fewer had live-born children compared to their brothers (Green et al., 2003), but no excess birth defects or other health problems were identified in their offspring. Moreover, no unusual rates of cancer are seen in the children of cancer survivors, except in families with inheritable cancer syndromes (Winther et al., 2004). Theoretically, a genetically defective sperm would not be capable of fertilizing the oocyte or an embryo produced with a defective sperm would fail to develop. Therefore, there is no basis to recommend that male cancer survivors forego fatherhood or to advocate conception using cryopreserved sperm obtained before cancer treatment versus fresh sperm produced years later out of concern over the risk of birth defects or increased rates of cancer in offspring.

FERTILITY PRESERVATION OPTIONS: SPERM BANKING BEFORE CANCER TREATMENT

Although banking sperm before cancer treatment has been an option for many years, its practicality was limited in the past. Some sperm always died during freezing, and few cancer patients had semen of high enough quality to achieve success with the infertility treatments that were available. Fortunately, since IVF with intracytoplasmic sperm injection (ICSI) became available in 1992, conception often only requires that small numbers of live sperm survive banking (Shin, Lo, & Lipshultz, 2005). The embryologist can choose one normal-appearing sperm to inject into each oocyte obtained for IVF. Additionally, one ejaculate can be divided into small vials for use in several IVF cycles. Another barrier was overcome when researchers discovered that semen of adequate quality for banking could be obtained when samples were collected on consecutive days, rather than after 36 hours of abstinence as previously recommended (Agarwal, Sidhu, Shekarriz, & Thomas, 1995). Therefore, even men with an urgent need to begin cancer treatment can

often collect one or two samples before initiating therapy. Moreover, since sperm from cryopreserved semen may remain viable for many years (sperm has been successfully used after being frozen for up to 25 years), banking is increasingly offered to adolescent cancer patients (Wallace et al., 2005).

Because it is difficult to predict whether any individual will recover spermatogenesis after cancer therapy, the Ethics Committee of the American Society for Reproductive Medicine (2005) has endorsed the recommendation that any man whose fertility is at risk be offered sperm banking. In countries like Norway and Japan, where sperm banking is part of socialized medical benefits, about one half of men decide to bank sperm (Magelssen et al., 2005; Saito, Suzuki, Iwasaki, Yumura, & Kubota, 2005). Japanese men have reported overwhelmingly that banking sperm helped them cope emotionally with their cancer (Saito et al., 2005). In contrast, only approximately one fourth of eligible men in the United States bank sperm (Chung et al., 2004; Schover, Brey, Lichtin, Lipshultz, & Jeha, 2002a). In a survey of over 200 young male patients seen in major cancer centers, only one half recalled being told about sperm banking (Schover et al., 2002a). This is particularly unfortunate because, among men interested in having children in the future, the most common reason for not banking sperm, cited by 25%, was lack of information. Men were more likely to bank sperm if they were referred by a physician and if they were childless at the time of their cancer diagnosis. However, a companion survey of oncology physicians revealed that despite endorsing the idea of discussing sperm banking with all eligible men, 48% of physicians either never mentioned it or did so less than 25% of the time (Schover, Brey, Lichtin, Lipshultz, & Jeha, 2002b). One half of these physicians cited a lack of time to discuss the topic in a busy clinic, not knowing where to find a convenient sperm bank, and believing that most patients could not afford the fees; in fact, only 7% of male patients cited cost as a factor in deciding not to bank sperm (Schover et al., 2002a).

ADDITIONAL OPTIONS TO PRESERVE MALE FERTILITY

Efforts to protect spermatogenesis during chemotherapy have included the use of gonadotropin-releasing hormone (GnRH) analogues with or without testosterone, but despite promising results in animals, human trials have been disappointing (Shetty & Meistrich, 2005). For prepubertal boys, a future option may be to harvest spermatogonial stem cells from the immature testes and cryopreserve them either in a suspension that could later be injected back into the testes to repopulate the sperm-producing tubules, or embedded in tissue that could later be autografted back into the body or even xenografted onto a mouse so mature sperm cells could be harvested for infertility treatment (Orwig & Schlatt, 2005). These techniques are not yet ready for clinical trials in humans.

When cancer survivors are azoospermic, exploratory microsurgery can sometimes identify islands of spermatogenesis, yielding sperm for IVF-ICSI (Chan, Palermo, Veeck, Rosenwaks, & Schlegel, 2001). This procedure is called testicular sperm extraction and is available for males before or after puberty, although it is experimental for prepubertal boys. Additional parenthood options available for male cancer survivors with

continued on page six

Fertility Considerations for Women with Breast Cancer

Kathy Lostritto, RN

Advances in the treatment of breast cancer have resulted in remarkable improvements in survival rates; consequently, issues regarding survivorship have increasingly become a focus of research and discussion. Much of this research has focused on the long-term consequences of breast cancer treatments and their impact on quality of life.

More often than not, a critical issue facing women in their childbearing years who are diagnosed with breast cancer is the loss of reproductive function as a result of cancer treatment. The diagnosis of cancer alone is devastating, but the thought of never being able to conceive a child using one's own eggs is often unbearable for these women. In addition to the direct effects of chemotherapy on fertility, patients receiving hormonal therapy will need to delay their pregnancy plans. These plans may then be further delayed due to concerns about the safety of pregnancy shortly after treatment and the risks of breast cancer recurrence.

An increasing awareness of the effects of cancer treatment on fertility has resulted in a growing number of premenopausal women seeking information on how to preserve fertility prior to breast cancer treatment. Moreover, fertility preservation for women diagnosed with cancer is an emerging field of reproductive medicine.

Recent advances made in the cryopreservation of oocytes, embryos, and ovarian tissue, and results of alternative methods of ovarian stimulation for IVF are creating opportunities for women diagnosed with breast cancer to preserve fertility prior to undergoing chemotherapy without compromising survival (Oktay, Buyuk, Libertella, Akar, & Rosenwaks, 2005; Oktay, Kan, & Rosenwaks, 2001; Sonmezer & Oktay, 2004).

BREAST CANCER TREATMENT AND FERTILITY RISKS

Neither breast cancer surgery to remove the primary tumor nor radiation therapy (which generally does not include the pelvic region) should affect the fertility of breast cancer patients. However, infertility will result from surgical oophorectomy (i.e., surgical removal of the patient's ovaries), which is a treatment option for selected premenopausal patients with hormone receptor-positive breast cancer (Thewes et al., 2005). Fortunately, the advent of agents that suppress ovarian function is obviating the need for surgical oophorectomy in a growing number of cases.

Women with breast cancer, who are receiving chemotherapy may experience temporary or permanent amenorrhea and are at the greatest risk of fertility impairment. Women may become menopausal immediately after chemotherapy or later, but will likely develop early menopause. The risk of chemotherapy-induced amenorrhea and/or permanent menopause varies according to the chemotherapy agent used, its dose, and the patient's age. For instance, cyclophosphamide is one of the chemotherapy agents most likely to induce amenorrhea, especially when used in regimens such as classic CMF (cyclophosphamide, methotrexate, and 5-fluorouracil) and CEF (cyclophosphamide, epirubicin, and 5-fluorouracil; Minton & Munster, 2002). Goldhirsch and colleagues (1990) found a 33% incidence of amenorrhea in patients under 40 years of age receiving classic CMF for 6 months; this incidence increased to 81% in patients aged 40 or over. A randomized clinical trial in premenopausal women with breast cancer showed amenorrhea rates of 51% associated with CEF and 42.6% associated with CMF (Fornier, Modi, Panageas, Norton, & Hudis, 2005). Rates of amenorrhea associated with four cycles of AC (anthracycline and cyclophosphamide) were found to

be 50% to 60% for women over 40 years of age and 10% to 15% for patients under the age of 40 (Partridge, 2004). Limited data exist on the risks of amenorrhea for patients receiving dose-dense regimens, more than four cycles of AC, or taxane-containing regimens. Recently, a clinical trial involving premenopausal women with breast cancer aged 40 or under who received four cycles of AC followed by a taxane reported an amenorrhea rate of 15% (Fornier et al., 2005).

Hormonal therapies for breast cancer do not appear to have a permanent effect on fertility; however, pregnancy must be delayed during treatment with tamoxifen and other agents that suppress ovarian function (Thewes et al., 2005). Unfortunately, the woman continues to move toward natural menopause during that interval.

FERTILITY PRESERVATION OPTIONS AND PREGNANCY

Premenopausal women diagnosed with breast cancer usually have a hiatus of 4 to 6 weeks between surgery and initiation of chemotherapy. This provides time to investigate fertility preservation options (see *Fertility Preservation Options for Women with Cancer* on page 1) and evaluate whether they are appropriate. It is also adequate time for controlled ovarian stimulation for oocyte or embryo cryopreservation. Patients who do not have enough time to go through an IVF cycle to cryopreserve oocytes and/or embryos may consider cryopreservation of ovarian tissue, which remains experimental at this time (Oktay et al., 2001; Sonmezer & Oktay, 2004).

Any patient planning to proceed with fertility preservation should consult a reproductive endocrinologist. Blood work will be performed for the patient and her partner, if applicable, and an orientation to the IVF process will be given. If IVF with ovarian stimulation is chosen, the patient should receive instruction on subcutaneous injections

to stimulate the ovaries. Financial information should also be supplied prior to undergoing IVF because the decision to continue with the process may depend on the patient's financial status. Many insurance companies do not cover IVF, especially when the diagnosis is cancer rather than infertility. Because fertility preservation procedures represent a financial hardship for many candidates, information about grant programs, such as the Fertile Hope-Sharing Hope program, should also be given to the patient.

The method used to obtain oocytes for IVF and/or freezing is an important consideration for patients with breast cancer. Hormones are often administered (IVF with stimulation) to stimulate the generation of an increased number of oocytes from the ovaries. This raises the estradiol level and poses a risk for women with breast cancer, because tumor proliferation and invasion can be induced by estrogen (Oktay, Buyuk, Rosenwaks, & Rucinski, 2003; Oktay et al., 2005). Therefore, many women with breast cancer are offered IVF without stimulation, which will result in only one naturally generated oocyte for collection each month. Unfortunately, because the interval between surgery and initiation of chemotherapy is 4 to 6 weeks, most breast cancer patients have only one cycle to obtain one egg for IVF. As many oocytes or embryos should be frozen as possible prior to starting chemotherapy.

Recently, results of a prospective, controlled trial evaluating alternative ovarian stimulation protocols for patients with breast cancer were published (Oktay et al., 2005). These protocols used either tamoxifen (n=11) or letrozole (n=11) in combination with a recombinant follicle-stimulating hormone (FSH) to develop multiple oocytes for retrieval. These approaches were compared to ovarian stimulation with tamoxifen alone (n=12). A control group included women with breast can-

Patient Focus

Why I Wanted to Survive

Lindsay Nohr Beck

Founder and Executive Director, Fertile Hope

As I write this article, I am 4 months pregnant. This has changed my perspective on cancer-related infertility. As you will see from my story, fertility was always critically important to me, but it wasn't until my husband and I heard our baby's heartbeat for the first time that it became clear—this is why I wanted to survive!

I was first diagnosed with cancer at the age of 22, the day after running a marathon. I thought I was the healthiest I had ever been. Clearly, I was wrong. I was successfully cured with aggressive radiation, but 1.5 years later the cancer returned and had spread to my lymph nodes. The second time, I had the wisdom of knowing I could get through the grueling short-term side effects of cancer treatment and was much more apprehensive about long-term effects. I was less preoccupied with hair loss and nausea and more concerned about survivorship issues like infertility. I wanted to know what I would have to deal with forever.

Thanks to a brilliant team of doctors, the surgery to remove one third of my tongue was a success. However, to my surprise, the follow-up treatment would involve an exhausting 3 months of chemotherapy and 6 additional weeks of radiation. Everything changed with the prospect of chemotherapy.



Before treatment, I researched and developed a laundry list of questions for my oncologist. I wanted to know everything about how the chemo would affect my body. After a thorough discussion with my oncologist, I felt relieved that he hadn't mentioned infertility. I figured if he hadn't mentioned it, it wasn't an issue. Later, though, it began to gnaw at me. I had to know for sure, and I knew if I didn't ask I would kick myself later. So, I called him and popped the question: "Will the chemotherapy make me infertile?" His answer shocked me: "Yes, there is a good chance it will make you infertile." I was obviously upset by his response and he scrambled to put me at ease. He told me not to worry, the odds were in my favor, and then he started talking about Lance Armstrong. He went on and on about how Lance had some of the same drugs I was going to have and that he just had a bouncing baby boy.

I almost choked. I was irate that in our previous discussion he decided not to mention infertility. What gave him the right to pick and choose which side effects he told me about and which ones he didn't? And, if he was hiding this, what else was he hiding? Then I remembered an article I had read in the waiting room about Lance Armstrong and became furious. That month a fashion magazine had printed an article noting how grateful Lance was that he had the foresight to bank his sperm—he was infertile! I didn't know what to do. I was beside myself. For me, the thought of being sterile was more devastating than the cancer diagnosis itself.

Naively, until then, I had never thought of my situation as a matter of life and death. I beat cancer before and was confident I would again. That all changed, however, when I called my surgeon and told her that I refused to have chemo in the name of fertility. She kindly, but frankly, told me that she wanted me alive in 5 years to think about a family instead of dead because I didn't undergo treatment. The question was clear: life or motherhood? The answer was obvious, but infertility was still unacceptable for me. I hated the idea of being a 24-year-old, single, infertile cancer survivor. There had to be something I could do. After all, I reasoned, men can bank their sperm. There had to be an equivalent for me, right?

Wrong. There isn't an equivalent to sperm banking for women, but there are options, and I began a quest to find them. I wasn't particularly well

cer who were not undergoing IVF (n=31). Tamoxifen, a well-known medication for the treatment and prophylaxis of breast cancer, was originally used as an ovulation-induction medication (Klopper & Hall, 1971). The rationale for its use in women with breast cancer undergoing ovarian stimulation for IVF is that it stimulates multiple oocytes to grow while blocking the tumor's estrogen receptors, which makes it safe for breast cancer patients. Recently, letrozole, an aromatase inhibitor, has been used for the same purpose. Letrozole suppresses the estradiol level by up to 90% and has been used as an alternative to tamoxifen.

Results of the study showed that, in comparison with tamoxifen alone, patients undergoing IVF using tamoxifen plus FSH or letrozole plus FSH had more mature oocytes and more embryos available to freeze (Figure 1; Oktay et al., 2005). Differences in embryo generation between women receiving tamoxifen plus FSH and those receiving letrozole plus FSH were not statistically significant. Peak estradiol level was significantly lower in patients receiving tamoxifen alone or letrozole plus FSH when compared to tamoxifen plus FSH. However, the levels of estrogen produced with tamoxifen plus FSH were not higher than estrogen levels that result from treatment with tamoxifen for breast cancer. Finally, although the study was not randomized and the follow-up is short at this point, the rates of breast cancer recurrence between patients who underwent IVF and those in the control group were not different.

Although these new ovarian stimulation protocols are promising, further research is needed on the safety of ovarian stimulation for IVF, the influence of tamoxifen or letrozole on chemotherapy results and the quality of oocytes generated, and the rates of pregnancy and breast cancer outcomes in women undergoing IVF (Partridge & Winer, 2005). Therefore, women with breast cancer must be informed about the limitations of available data on stimulating-cycle IVF thus far, so they

are able to weigh the risks and benefits when making their choices regarding fertility preservation options.

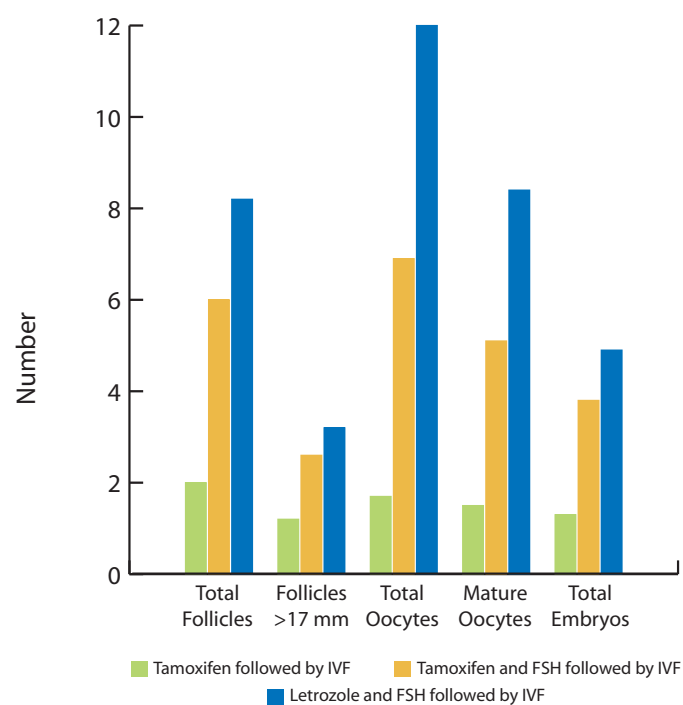
An experimental fertility preservation option in premenopausal women with breast cancer is treatment with GnRH analogues (e.g., leuprolide). These agents create a reversible prepubertal state in premenopausal women which some data suggest may protect the ovaries against the effects of chemotherapy. In a small clinical study, the effects of leuprolide were evaluated in 24 premenopausal women with early-stage breast cancer receiving AC or AC followed by paclitaxel (Fox, Scialla, & Moore, 2003). Indeed, after chemotherapy, menses resumed for the vast majority of patients, but few pregnancies were observed; only one live birth had occurred at the time of the report. Three women required fertility treatments, which were unsuccessful. Therefore, the benefits of GnRH analogues in fertility preservation are controversial and treatment with these agents remains experimental.

Finally, the safety of pregnancy after breast cancer treatment is an important consideration for survivors. Most data from clinical trials suggest that pregnancy after treatment for breast cancer does not increase the risks of recurrence or metastatic disease (Wood, Muss, Solin, & Olopade, 2005). However, for patients with a high risk of recurrence or metastatic disease, pregnancy complicates future treatment. In these cases, an interval of 3 to 5 years after treatment of the primary disease (the most likely time for cancer recurrence) before becoming pregnant may be appropriate and should be discussed with the patient (Wood et al., 2005). Generally, pregnancy within 6 months after chemotherapy cessation is not recommended due to the possibility of miscarriages and birth defects.

CONCLUSIONS

The survival rate of women with breast cancer is on the rise, but many young premenopausal women are poorly counseled on the effect of chemotherapeutic agents on the ovaries

Figure 1. Results of Ovarian Stimulation Protocols in Breast Cancer Patients



Abbreviations: IVF = in vitro fertilization; FSH = follicle-stimulating hormone. (Oktay et al., 2005)

and the possibility of temporary or permanent amenorrhea, early menopause, and infertility. Receiving a breast cancer diagnosis is a traumatic experience, and dealing with the possibility of premature menopause and infertility is an additional significant stressor for premenopausal women with breast cancer. Therefore, although the health and survival of the patient is always the most important aspect of cancer treatment, consideration should be given to the emotional issues encountered by breast cancer survivors, and fertility preservation can be among the most critical of these issues.

Many advances have been made in reproductive medicine that may protect the health of breast cancer patients and still provide them with the possibility of future pregnancies. Not every woman is a candidate for fertility preservation, but information on the options should be given to every woman diagnosed with breast cancer. A discussion between the oncologist

and a reproductive endocrinologist is important for both physicians to understand the steps of fertility preservation procedures. Although oocyte and ovarian tissue cryopreservation are still experimental, embryo cryopreservation is available. Considerations regarding ovarian stimulation and IVF should be discussed with the patient. Continued research is needed on the risk of breast cancer recurrence in patients undergoing these procedures.

Breast cancer survivors experiencing fertility problems after chemotherapy should be referred to a reproductive endocrinologist for a full work-up to check ovarian function. If ovarian function is decreased, the patient may benefit from an IVF cycle to help stimulate the follicles within the ovaries. This gives the cancer survivor a chance to conceive using her own eggs. Adoption or the use of donor eggs or embryos are options for women who

continued on next page

connected in the medical world, didn't have the luxury of extra time or energy, and had no idea where to start, but I refused to give up.

As a single young woman, embryo freezing was not an option for me. I didn't have a partner and the idea of donor sperm was overwhelming at the time. I wanted to freeze my eggs. Through sheer persistence, dedication, and fear, I proceeded to question my healthcare team, call fertility clinics, scour the Internet, and reach out to cancer and fertility organizations, but I still came up empty handed. Even worse, everything I heard was discouraging and misleading, if not wrong. I was told over and over again: "you don't have time; fertility drugs cause cancer; egg freezing is not possible," and so on.

I found several organizations that addressed infertility and even more that addressed cancer, but nothing that addressed both—absolutely nothing. Then, one afternoon I was watching a movie in which one of the characters stated she was going to "harvest her eggs," and I thought, if it was in the movie, it had to exist, and I had to find it!

With a renewed (albeit potentially false) hope, I started repeatedly calling clinics in my area. After several calls to Stanford Medical Center, I was eventually told that they had an egg freezing program, but that it was only for young cancer patients. I was thrilled. For the first time in my life, I was happy to be the "young cancer patient!"

Time was of the essence. I was scheduled to start chemotherapy in 2 weeks, and egg freezing takes approximately 12 to 14 days. I was immediately examined, advised of the costs, risks, and procedural details, and sent home with a bag of medicine. After 2 weeks of self-administered shots, intense side effects, and an outpatient surgical procedure, I had 29 eggs safely stored for future use. I then underwent chemotherapy and radiation as scheduled with a new sense of optimism, strength, and excitement for the future. Despite all the appointments, medications, needles, and side effects, I relished anything that had to do with harvesting my eggs. It was the first positive in a long list of negatives. I now had a reason to fight, to live. Three months later I completed treatment and was relieved to have my eggs waiting in the wings as a means of living the life I had always imagined.

I was extremely lucky. First and foremost, I discovered my risks before starting treatment. And second, although the information was almost

impossible to find, the treatments were intense, and insurance didn't pay for them, I was able to preserve what was sacred to me—my fertility. After treatment, however, I realized just how lucky I was to know my risks and have the chance to preserve my fertility. As astounding as it sounds, most people, including cancer patients and survivors, do not know that chemotherapy, radiation, and surgery all have the potential to cause permanent infertility, let alone that there are several parenthood options available before, during, and after cancer treatment. Although up to 90% of patients diagnosed with cancer during their reproductive years are at risk for permanent infertility from their treatments, less than 10% of oncologists inform them about their risks and options.

My experience left me wondering how many people slip through the cracks, how many people discover the repercussions of their treatment after the fact, and why no one was doing anything about what seemed to be a gaping void in the care of cancer patients. It was inconceivable to me that so many patients were being left unaware, uneducated, and unknowingly infertile.

I felt as if I had a secret I could not bear to keep, so I founded Fertile Hope—a national nonprofit organization that provides reproductive information, support, and hope to cancer patients whose medical treatments present the risk of infertility. Through awareness, education, financial assistance, research, and support programs, Fertile Hope is dedicated to addressing the reproductive needs of cancer patients.

Now you know the secret too. You know that cancer treatment can cause infertility and premature menopause. You know that more fertility preservation options are available now than ever before. You know that parenthood options exist after cancer. With this knowledge, I encourage you to share the secret. Please help ensure that all patients understand their risks and are able to make educated and timely decisions about their future fertility.

Many cancer-related problems will take years to solve; however, in comparison, cancer-related fertility impairment is easy. There are risks and there are solutions. We just need to work together to bridge the gap and solve the problem. The impact will be profound—you will have given patients like me another reason to survive!

Fertility Preservation Options for Women with Cancer (continued)

Oocyte Cryopreservation

Recent advances in cryobiology have made oocyte cryopreservation possible. Cryopreserving unfertilized oocytes has many theoretical advantages over embryo cryopreservation. Women who do not have a partner available for embryo creation or those who find the cryopreservation and banking of embryos ethically objectionable may find the option of freezing unfertilized oocytes attractive. Furthermore, cryopreserving oocytes cannot result in a custody issue because the woman alone is in control of their use. However, oocyte cryopreservation must still be considered experimental at this time. As previously stated, oocytes are very large cells with a high water content; ice crystals that form during the cryopreservation process can fatally injure the cell. Improved cryobiology techniques such as vitrification result in rapid freezing with no ice crystal formation, thereby increasing the number of oocytes that survive the process (Nawroth et al., 2005). Oocyte cryopreservation has resulted in small numbers of live births; as of December 2004, more than 100 live births resulting from frozen oocytes were reported (Ethics Committee of the American Society for Reproductive Medicine, 2005). As more centers offer this procedure and more experience is accumulated, this number will likely increase.

Ovarian stimulation and oocyte harvesting for oocyte cryopreservation are identical to the processes involved with embryo cryopreservation and require

several weeks. Following harvest via transvaginal needle aspiration, the oocytes are immediately cryopreserved and stored within the assisted reproductive technology laboratory. When pregnancy is desired, presumably after the threat of cancer has passed, fertilization with partner or donor sperm can occur. Fertilization of cryopreserved oocytes, however, cannot proceed through conventional IVF. The outer surface of the oocyte is damaged during cryopreservation, preventing the sperm from penetrating the cell on its own. Intracytoplasmic sperm injection (ICSI) is necessary for fertilization. During ICSI, a single sperm is injected directly into the oocyte, greatly increasing the probability of fertilization.

The pregnancy rates for cryopreserved oocytes are lower than for embryos. Large numbers of harvested oocytes are therefore necessary to increase the probability of successful pregnancy. The shelf life of cryopreserved eggs is unknown, although theoretically the extremely cold temperatures used for storage (-196°C) should prevent any damage over time. Costs involved with oocyte cryopreservation are high, averaging between \$6,000 and \$10,000, and typically are not covered by health insurance.

Ovarian Tissue Cryopreservation

For ovarian tissue cryopreservation, an ovary or portion of an ovary is surgically removed. The outer surface of the ovary, called the cortex, is then further divided into smaller strips, cryopreserved, and stored. When the

threat of cancer recurrence has passed, the strips are surgically transplanted back into the patient. The strips can be attached to the remaining ovary or relocated to a more superficial and accessible area in the abdomen.

Ovarian tissue cryopreservation, if successful, has numerous advantages over oocyte or embryo cryopreservation. No ovarian stimulation is required and removal of the ovary can be accomplished via a laparoscope. This obviates the long delays required to harvest oocytes, thus making this procedure feasible for patients with aggressive malignancies in need of immediate therapy. Pubertal status of the patient is not an issue, so the procedure can be offered to very young cancer patients. The transplantation of ovarian cortex strips returns follicles and oocytes to the patient, thereby restoring estrogen production. A very real concern involving ovarian tissue cryopreservation is the possibility of cancer cells being transferred back to the patient along with the ovarian tissue. Certain malignancies, particularly hematologic diseases like leukemia and lymphoma, are known to invade the ovary. Protocols to screen the tissue prior to its return to the cured cancer patient are critical and must be developed.

Unfortunately, ovarian tissue cryopreservation has not yet produced satisfactory success rates, and should still be considered a highly investigational procedure. Nevertheless, successful ovarian tissue cryopreservation and retransplantation have been reported (Meirow et al., 2005; Oktay & Karlikaya, 2000). Ovarian function with cyclic follicular development has

been restored for some patients but early reports indicate only short-term viability of the transplanted tissue. Recently, two separate groups of investigators have reported live births believed to originate from cryopreserved ovarian transplants in cancer survivors (Donnez et al., 2004; Meirow et al., 2005; Wallace & Pritchard, 2004). Although ovarian tissue cryopreservation remains experimental, continued research will be aimed at improving the understanding and use of this new technology.

CONCLUSIONS

Fertility preservation for women with cancer has no easy answers at this time. Oncologists continue to search for less toxic modes of therapy, but change occurs slowly and cure of the primary malignancy must take precedence. Cryopreservation of embryos, oocytes, and ovarian tissue may be a possibility for many patients and should be explained and offered to them when appropriate. As cure rates for cancer continue to improve, more attention is appropriately being focused on quality of life. Infertility must never be viewed as an inconvenience; it should instead be considered a potentially devastating side effect of treatment. Organizations such as Fertile Hope and the Lance Armstrong Foundation have helped focus public attention on this problem. Nurses can help patients and families by providing up-to-date, accurate, and helpful information to women newly diagnosed with cancer.

The Impact of Cancer on Men's Fertility (continued)

impaired fertility after cancer treatment include the use of donor sperm and adoption.

INFERTILITY TREATMENT FOR MALE CANCER SURVIVORS

Until recently, less than 10% of cancer patients who banked sperm used their samples for infertility treatment, but this rate appears to be increasing (Agarwal et al., 2004; Chung et al., 2004). Live birth rates resulting from assisted reproduction using cancer patients' cryopreserved samples are excellent and at least equal to the rates achieved with the use of samples from men with impaired fertility from other causes (Revel et al., 2005). Although IVF-ICSI produces the highest success rate per cycle of treatment, the less expensive intrauterine insemination technique (with or without hormonal stimulation to induce multiple ovulations in the female partner) can be used for men whose semen samples contain over 2 million sperm per milliliter after freezing and thawing (Agarwal & Allamaneni, 2005; Chung et al., 2004; Revel et al., 2005; Schmidt et al., 2004).

Men usually discontinue storage of cryopreserved samples if they have conceived all the children they desire or have agreed to discard samples upon their death (Hallak, Sharma, Thomas,

& Agarwal, 1998), but some men prefer to will their samples to a family member who might use the sperm to conceive a posthumous child (Chung et al., 2004). Very few wives who consider conceiving posthumous children actually carry out their plan, but all men should create an advance directive stating their wishes regarding the cryopreserved samples (Bahadur, 2002; Ethics Committee of the American Society for Reproductive Medicine, 2005).

CONCLUSIONS

Men with cancer may suffer impaired fertility due to either the malignant process itself or cancer therapy. Although most oncologists recommend allowing an interval of 6 to 12 months after cancer treatment to attempt conception, there is no evidence that offspring of male cancer survivors exhibit more birth defects or are otherwise less healthy than offspring of men who have never had cancer. Sperm banking should be offered to any man facing fertility risks due to cancer treatment. Additional options to preserve fertility in male cancer patients include harvesting and cryopreserving spermatogonial stem cells from the immature testes (for prepubertal boys) and testicular sperm extraction.

Fertility Considerations for Women with Breast Cancer (continued)

are permanently menopausal after chemotherapy.

All fertility risks associated with cancer treatment and available fertility preservation options must be discussed with breast cancer patients prior to initiation of chemotherapy. Oncology nurses play an important role in this setting, and should work with the rest

of the healthcare team to inform these women about all available options and provide emotional support for surviving cancer and maintaining quality of life during and after treatment.

Pharmaceutical Glossary

Generic Name	Brand Name
Bleomycin	Blenoxane®
Busulfan	Busulfex®
Carmustine	BiCNU®
Chlorambucil	Leukeran®
Cisplatin	Platinol®
Cyclophosphamide	Cytoxan®
Dacarbazine	DTIC-Dome®
Doxorubicin	Adriamycin®
Epirubicin	Ellence®
Goserelin	Zoladex®
Letrozole	Femara®
Leuprolide	Lupron®
Lomustine	CeeNU®
Melphalan	Alkeran®
Methotrexate	Trexall™
Nitrogen mustard	Mustargen®
Procarbazine	Matulane®
Tamoxifen	Nolvadex®
Temozolomide	Temodar®
Thiotepa	Thioplex®
Vinblastine	Velban®

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Project ID: 202 news

Current Topics in Cancer Fertility
FOR ONCOLOGY NURSES

POST-TEST QUESTIONS FOR CURRENT TOPICS IN CANCER: FERTILITY (PLEASE RECORD THE CORRECT ANSWERS IN THE ANSWER KEY ON PAGE 8)

There are no fees for participating and receiving 1.2 nursing contact hours for this activity. During the period April 2006, through April 2008, participants must complete the posttest (below) by recording the best answer to each question in the answer key on page 8. Once you have finished your test and completed the subsequent evaluation form, please send your responses to us. Your test will be reviewed and if you receive a passing grade of 70% or better (5 out of 7 questions), a certificate of completion will be mailed to you within 3 weeks.

- All of the following cancer treatments have the potential to cause premature ovarian failure EXCEPT:
 - High-dose cyclophosphamide therapy
 - Pelvic radiation
 - Bone marrow transplant with a total-body irradiation preparative regimen
 - Radiation administered to areas above or well below the pelvis
- Which of the following have been used or investigated as fertility preservation options for female cancer patients?
 - Oocyte cryopreservation
 - Ovarian tissue cryopreservation
 - Embryo cryopreservation
 - Ovarian transposition
 - All of the above
- A 30-year-old patient is diagnosed with breast cancer and is facing chemotherapy and possible tamoxifen for 5 years. Special considerations that should be discussed with the patient regarding the effects of cancer treatment on her fertility and fertility preservation options are:
 - The risk of amenorrhea and premature menopause associated with chemotherapy regimens
 - The recommendation of delaying pregnancy during endocrine therapy
 - The safety of ovarian stimulation for in vitro fertilization (IVF)
 - All of the above
- Which of the following is CORRECT?
 - The incidence of chemotherapy-induced amenorrhea in patients with breast cancer is higher in women under the age of 40 than in women over 40 years old
 - Four cycles of AC chemotherapy is associated with a 50% risk of amenorrhea in patients under the age of 40
 - Alternative ovarian stimulation protocols for IVF include the use of tamoxifen or letrozole with a recombinant follicle-stimulating hormone
 - The use of GnRH analogues is a well-established fertility preservation option for women with breast cancer
- A cancer treatment that causes permanent infertility in most men is:
 - ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) chemotherapy
 - Total-body irradiation
 - Brachytherapy for prostate cancer
 - GnRH analogue plus testosterone
- Infertility is particularly common in men treated for testicular cancer because:
 - They often have abnormalities in both testicles that affect sperm production
 - They often develop cancer in both testicles
 - Their chemotherapy is especially likely to damage fertility permanently
 - All of the above
- DNA damage is most likely to be found in sperm:
 - At the time of cancer diagnosis
 - One year after chemotherapy
 - In the weeks just after chemotherapy or pelvic radiotherapy
 - Both A and C

EVALUATION FORM—CURRENT TOPICS IN CANCER: FERTILITY

The Institute for Medical Education & Research (IMER) respects and appreciates your opinions. To assist us in evaluating the effectiveness of this activity and to make recommendations for future educational offerings, please take a few minutes to complete this evaluation form. You must complete this evaluation form to receive acknowledgement of participation for this activity.

5 = Outstanding	4 = Good	3 = Satisfactory	2 = Fair	1 = Poor
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EXTENT TO WHICH PROGRAM ACTIVITIES MET THE IDENTIFIED PURPOSE

- Provide education to oncology nurses on fertility risks and preservation options for cancer patients and survivors. 5 4 3 2 1

EXTENT TO WHICH PROGRAM ACTIVITIES MET THE IDENTIFIED OBJECTIVES UPON COMPLETION OF THIS ACTIVITY, PARTICIPANTS SHOULD BE ABLE TO:

- Identify the risk of infertility in cancer survivors of reproductive age 5 4 3 2 1
- Describe fertility options currently available to men and women 5 4 3 2 1
- Discuss fertility considerations for female breast cancer survivors 5 4 3 2 1

OVERALL EFFECTIVENESS OF THE ACTIVITY

- Was timely and will influence how I practice 5 4 3 2 1
- Will assist me in improving patient care 5 4 3 2 1
- Fulfilled my educational needs 5 4 3 2 1
- Avoided commercial bias or influence 5 4 3 2 1

IMPACT OF THE ACTIVITY

The information presented (check all that apply):

- Reinforced my current practice/treatment habit
- Will improve my practice/patient outcomes
- Provided new ideas or information I expect to use
- Enhanced my current knowledge base

Will the information presented cause you to make any changes in your practice?

- Yes No

If Yes, please describe any change(s) you plan to make in your practice as a result of this newsletter:

How committed are you to making these changes?

(Very committed) 5 4 3 2 1 (Not at all committed)

Additional comments about this activity:

Continued on page eight

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FUTURE ACTIVITIES

Do you feel future activities on this subject matter are necessary and/or important to your practice?

- Yes No

Please list any other topics that would be of interest to you for future educational activities:

EFFECTIVENESS OF THE INDIVIDUAL FACULTY MEMBERS

Faculty Members	Knowledge of Subject Matter					Clarity of Content				
	5	4	3	2	1	5	4	3	2	1
Marcia Leonard, RN, PNP	5	4	3	2	1	5	4	3	2	1
Leslie R. Schover, PhD	5	4	3	2	1	5	4	3	2	1
Kathy Lostritto, RN	5	4	3	2	1	5	4	3	2	1

I certify my actual time spent to complete this educational activity to be:

- I participated in the entire activity and claim 1.2 contact hours.
- I participated in only part of the activity and claim _____ contact hours.

REQUEST FOR CREDIT

Name _____

Degree _____

Specialty _____

Organization _____

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Post-test answer key

1	2	3	4	5	6	7

The following items do not need to be completed to receive acknowledgement of participation in this activity.

Follow-up

- Years in practice:
- <2 years
 - 2-5 years
 - 6-10 years
 - >10 years

Educational background (highest degree):

- Associate/Diploma
- BSN
- MSN
- PhD
- Other _____

Primary functional area:

- Patient care
- Education
- Administration
- Research
- Other _____

Primary specialty:

- Chemotherapy/biotherapy
- Breast oncology
- GI oncology
- Hematology/BMT
- Pediatric oncology
- Radiation oncology
- Thoracic oncology
- Patient education
- Prevention/detection
- Palliative care
- Other _____

Do you prefer educational CE seminars or mail CE programs?

- Seminars
- Mail

I **most** prefer CE programs that are:

- On a Web site that I can visit
- Audio CDs
- Print materials
- Teleconferences
- CD-ROMs (audio plus slideshow)

I **least** prefer CE programs that are:

- On a Web site that I can visit
- Audio CDs
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- CD-ROMs (audio plus slideshow)

As part of our ongoing quality-improvement effort, we conduct post-activity follow-up surveys to assess the impact of our educational interventions on professional practice. Please indicate your willingness to participate in such a survey:

- Yes, I am interested in participating in a follow-up survey
- No, I'm not interested in participating in a follow-up survey

Additional comments about this activity: _____