

Preconception and the Young Cancer Survivor

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Received: 21 November 2005 / Accepted: 20 April 2006 / Published online: 9 June 2006
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Keywords Preconception · Fertility preservation · Ovarian failure · Pregnancy after cancer

Introduction

While the diagnosis of cancer is not common in young men and women, cancer survivors younger than 40 are likely to be very concerned about the impact of their cancer on future fertility, their risk of cancer recurrence after treatment and risks to future offspring. It is estimated that 1 in 900 persons between 16 and 44 are cancer survivors [1], and that there are at least 250,000 women age 40 and younger who are breast cancer survivors in the United States. As cancer survival increases, the focus on quality of life issues increases. When questioned, at least 73% of young breast cancer survivors reported concerns about infertility due to cancer treatment, and 29% reported that this concern impacted their choice of cancer treatment [2].

Premature ovarian failure

In women, the options for preserving fertility and risk of ovarian failure depends on the age at the time the cancer is treated, the type and location of cancer, and the specific treatment chosen. Some treatments, such as bone marrow transplantation (BMT) are accompanied by very high rates (>99%) of ovarian failure [3]. Even for those women who resume normal menstruation after chemotherapy, premature ovarian failure (POF) is not uncommon [4], and the risk of

premature ovarian failure is 8-fold higher in cancer survivors [5]. The risk of POF increases with the woman's age, with less than 20% of women under 30 years experiencing POF, whereas most women older than 40 will become menopausal after chemotherapy [6].

POF and menopause are dependent on the type of therapy used. Rates of ovarian failure range from 15% for acute myelocytic leukemia (AML) to 50% for breast cancer, with the overall rate of ovarian failure of 34% [4]. The chemotherapy agents with the highest risk for ovarian failure were the alkylating agents. The higher the dose of these drugs, the higher the likelihood of ovarian failure.

Ovarian tissue damage is well documented with the use of radiation therapy. Radiotherapy is used for treatment of several cancer types affecting pre-menopausal women. The degree of damage to ovarian tissue is related to a woman's age, the total dose of radiation used, and the number of exposures. In one study, when the same total dose of radiation was delivered, exposure to multiple fractionated doses versus a single dose resulted in less damage to the ovaries [4]. When used in conjunction with chemotherapy, the risk of POF increases. Byrne et al. assessed the risk of premature ovarian failure in childhood cancer survivors and found the relative risk of early menopause was 9.2 for those treated with chemotherapy alone, and 27 for those treated with radiation plus chemotherapy [5].

Fertility preservation techniques

Although an increasing number of techniques have become available for the preservation of fertility, many are experimental and have not been tested in randomized controlled trials. Table 1 reviews the types of options available and their benefits and limitations.

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Table 1 Fertility preservation options for women with malignancies

Method	Benefits	Limitations
In vitro Fertilization (IVF)	Most successful, widespread	Delay of therapy, use of fertility medications
Frozen oocytes	No partner is needed	Difficult to preserve
Ovarian tissue preservation	Less tissue damage from freezing, can be used in pre-menarchal and young women	Experimental
Transposition of ovarian tissue	Less radiation exposure	Limited to women having radiation therapy
Pharmacological protection	Limit damage to ovarian tissue	Adequate prospective studies needed

In vitro fertilization (IVF)

The best-studied and most successful option for preserving fertility in female cancer patients is ovarian stimulation followed by IVF and embryo cryopreservation. Ovarian stimulation needs to occur prior to cancer therapy because treatment can adversely affect ovarian reserve and response. The pregnancy rate with frozen embryos is lower compared to fresh IVF embryo transfer. A meta-analysis by the American Society for Reproductive Medicine reviewed over 88000 cycles of assisted reproductive technology (ART) treatment. When fresh oocytes were used, a delivery rate of 41.8% was found in more than 6500 cycles analyzed, compared to a delivery rate of 18.6% for frozen embryos [7].

One concern about ovarian stimulation with IVF is that it requires a delay of therapy, which could impact growth rate of tumors and survival rates. In addition, concerns have been voiced that the medications used to stimulate ovarian production could impact on estrogen-receptor positive tumors such as breast carcinoma. Anti-estrogens, such as tamoxifen, or aromatase inhibitors, (e.g. letrozole), have both been used in ovarian stimulation in breast cancer patients to maintain low estradiol levels during IVF cycles.

Frozen oocytes

Frozen oocytes are more difficult to preserve, resulting in a lower survival, fertilization and pregnancy rates. Damage is in part due to ice formation during the freezing process. Unfertilized frozen oocytes have a low success rate for live birth (2% per oocyte) [8], although the rates are now increasing. Rapid freezing of eggs by vitrification limits damage, which improves oocyte survival. Using intracytoplasmic sperm injection (ICSI) increases the fertilization rate even further.

Ovarian tissue cryopreservation

For pre-menarchal girls, young women with POF, women that cannot delay therapy or those in whom high doses of fertility medications are contraindicated, ovarian tissue cryop-

reservation is offered in some centers. Unlike frozen oocytes, primordial follicles in ovarian tissue are smaller and have less follicular fluid, and therefore may be at less risk from damage from ice crystals that form during freezing. It is hoped that transplanting thawed ovarian tissue will result in the recovery of fertility. Transplantation should be used with caution in women with ovarian or metastatic cancer, to prevent transferring malignant cells back after treatment. This treatment is still considered experimental. Although success in animals has been demonstrated, transplantation of cryopreserved ovarian tissue has resulted in only two livebirths [9, 10].

Ovarian transposition

For women having pelvic radiation, transposition of ovarian tissue outside of the field of radiation successfully preserves ovarian function. The radiation dose to the transposed ovary is approximately 5–10% the level of the non-transposed ovary [11].

Pharmacological protection

To limit or prevent chemotherapy-induced POF, some centers use gonadotropin releasing hormone (GnRH) agonists to reduce gonadotropins. This results in mimicking a pre-pubertal state, because the ovary appears to be less sensitive to gonadotoxic drugs prior to menarche. Because dividing cells are more susceptible to damage from cytotoxic agents, ovarian follicular cells are vulnerable. The mechanism of protection by GnRH agonists is unknown. One prospective clinical case series found that 70 of 75 women (93%) co-treated with GnRH agonists and chemotherapy resumed cyclic ovarian function versus 38 of 82 women (46%) treated with chemotherapy alone [12]. Adequately controlled prospective studies still are required, although data from animal studies are promising. Anti-apoptotic agents, such as sphingosine-1-phosphate (SIP), have prevented radiation-induced oocyte loss in mice [13]. However, since apoptosis is needed for the treatment of cancer, this method faces some obstacles for implementation.

Male fertility

In men, sperm banking is routine and should be offered to all men prior to undergoing cancer treatment. When combined with intracytoplasmic sperm injection (ICSI), sperm banking should preserve fertility for almost all males. There is no increased risk for birth defects when sperm is banked prior to therapy [14, 15]. Even in azoospermic males, testicular sperm extraction (TESE) with ICSI has resulted in successful pregnancies. By 2005, 11 of 29 men with azoospermia that had used TESE with ICSI had achieved a pregnancy which resulted in a livebirth [16]. For pre-pubertal males, sperm banking is not available because there is no spermatogenesis. The possibility of cryobanking of testicular tissue is being explored [16, 17]. An increase in sperm aneuploidy is seen up to 18 months post-chemotherapy, so it has been suggested that a delay of conception for 12–18 months after therapy is completed is reasonable [18].

Pregnancy after cancer

Once a woman has recovered from cancer treatment, no clear guidelines exist about the length of time to wait before attempting to become pregnant.

Effect of cancer treatment on pregnancy

Once a cancer survivor achieves pregnancy, her health and the fetal health may be adversely affected by her prior treatment for cancer. Clinically significant heart disease occurs in 0.5–1% of women treated with anthracycline-based chemotherapy drugs, and may not develop until months or years after therapy is completed [19]. Also, women who have radiation to the left side of the abdomen or chest are at risk for heart damage, which could worsen during pregnancy or labor. Women with radiation to the abdomen or pelvic area or total body radiation are at increased risk for miscarriage, preterm birth and delivery of low birthweight infants [20]. A report from the Childhood Cancer Survivor Study (CCSS) did not show any increase in adverse pregnancy outcomes in women treated with most chemotherapy agents. However, an increased risk of stillbirth in women treated with abdominal radiation for Wilm's tumor has been noted [21].

Women who have completed treatment for breast cancer are often placed on selective estrogen receptor modulators (SERMs) such as tamoxifen to reduce the incidence of a second cancer. However, tamoxifen use during pregnancy is to be avoided because it is potentially teratogenic.

Effect of pregnancy on cancer

Some women are concerned that the hormonal changes from pregnancy may increase the risk of cancer recurrence, but pregnancy after breast cancer management does not increase the risk of cancer recurrence or cancer-related death [22, 23]. However, women who are carriers of *BRCA1* or *BRCA2* germline mutations and who have had a full-term pregnancy are at significantly higher risk of developing breast cancer by age 40 than mutation carriers who do not have children [24]. The risk for breast cancer is increased by 70% in the first 2 years after pregnancy for *BRCA2* carriers, but not *BRCA1* carriers [25].

Risk to offspring

Since cancer treatment by radiation and many chemotherapy agents are known to cause DNA mutations, cancer survivors are often concerned that the treatment may increase the risk for birth defects, genetic conditions or cancer in their offspring. Several studies have found no increased risk of congenital abnormalities in the offspring of cancer survivors. Epidemiologic data from Japanese survivors of the atomic bomb and their children did not show any evidence for new mutations. The CCSS also did not find any link between radiation therapy or chemotherapy for childhood cancer and genetic diseases or birth defects [26, 27].

Risk of cancer in offspring

No increased risk for childhood cancer was identified in the offspring of childhood cancer survivors, but additional follow-up is needed [26]. In rare instances, the childhood cancer may be hereditary, with a risk of passing on the mutated gene to the offspring. Some cancers, such as breast, colon or ovarian cancer, are more likely to be hereditary when the cancer occurs at an earlier age. For women with breast cancer diagnosed prior to age 40 and no other family history of early breast cancer, the risk of a mutation in one of the hereditary breast cancer genes, *BRCA1* or *BRCA2* is estimated to be at least 13% [28].

Summary

All women should be counseled about the impact of cancer treatment on fertility prior to undergoing chemotherapy, ovarian surgery or BMT, and offered fertility preservation options, of which ovarian stimulation with IVF is the most successful. Once women achieve pregnancy, the risk for birth defects or genetic conditions is not increased because of

either radiation or chemotherapy. Because treatment options may increase the risk for adverse pregnancy outcome, review of therapy records is essential for determining potential risk to the pregnancy. For most young cancer survivors, fertility can be preserved and a successful pregnancy achieved, but discussing these issues prior to treatment is essential.

Acknowledgement I would like to thank Dr. Herschel W. Lawson for his critical commentary.

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