

Understanding Fertility in Young Female Cancer Patients

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Abstract

Young women diagnosed with cancer today have a greater chance of long-term survival than ever before. Successful survivorship for this group of patients includes maintaining a high quality of life after a cancer diagnosis and treatment; however, lifesaving treatments such as chemotherapy, radiation, and surgery can impact survivors by impairing reproductive and endocrine health. Studies demonstrate that future fertility is a concern for many women diagnosed with cancer, but physician knowledge and attitudinal barriers can still prevent females from receiving care. Today, fertility preservation is an option for girls and women facing a cancer diagnosis, and emerging research is providing clinicians with an increasing number of reproductive and hormonal management tools. Physicians can play an important role in fertility by working closely with oncologists, providing patients with information about fertility preservation options prior to the start of cancer treatment, monitoring reproductive capacity after treatment, and working with cancer survivors to explore potential avenues to parenthood.

Introduction

MORE THAN 135,000 PEOPLE under the age of 45 years are diagnosed with cancer every year, and approximately one-half of these patients are women.¹ Currently, more than 70% of patients under the age of 45 who are diagnosed with cancer will survive more than 5 years after treatment.² Taken together, there are more than 270,000 survivors of pediatric cancer and more than one million survivors of young adult cancer in the United States today.³ Quality-of-life issues for these survivors, such as fertility, are gaining exposure in clinical and public realms. Many survivors hope to have a biological family; in fact, prior studies indicate that the process of surviving a cancer diagnosis may actually increase the desire to have children.⁴⁻⁵ However, the same life-saving treatments that increased the cancer survival rate can also cause immediate or premature infertility in cancer survivors.⁶⁻¹⁰ New technologies are emerging that allow young patients to preserve their fertility before they start treatment; however, discussions about the reproductive risks posed by cancer treatment and the options available to preserve fertility can be challenging in the period between diagnosis and the start of cancer treatment. Physicians treating women are in a unique position to discuss fertility preservation and reproductive options for cancer patients and survivors across the treatment spectrum. Recent research

indicates that many primary care physicians lack the awareness and exposure to current clinical literature on the reproductive impacts of cancer treatment.¹¹ As physicians will be caring for a growing population of young cancer survivors, it is important that they understand the effects of specific cancer treatments on fertility and the need for reproductive and hormonal management after cancer treatment. In addition, early referral to either a gynecologist or reproductive endocrinologist is recommended to ensure that women are counseled about fertility preservation options.

The Reproductive and Hormonal Effects of Cancer Treatment

Cancer treatments including surgery, chemotherapy, and radiation can affect fertility by impacting several biologic systems. The neuroendocrine axis, the immature and growing follicles within the ovaries, and the reproductive organs necessary for a woman to carry a pregnancy to term may all be impacted by cancer treatment.

Because the hormones released by the reproductive axis are also essential for overall growth and the health of other body systems, damage to the reproductive system in prepubescent girls may have long-term implications. Gonadal damage caused by chemotherapy or radiation may result in the omission, delayed onset, and abnormal development of

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secondary sex characteristics.¹² Furthermore, central nervous system radiation can result in either delayed or precocious puberty. It is important for pediatricians, gynecologists, and primary care providers to be aware of these post-treatment developmental concerns.

Radiation therapy

Radiation therapy may impact the future reproductive ability of cancer survivors in a number of ways depending on the cumulative dose of radiation, location of the treatment, and age of the patient.¹³ Women who receive abdominal or directed pelvic radiation at high doses are at greater risk for subsequent infertility. The ovarian reserve is sensitive to pelvic radiation, which may destroy the majority of immature ovarian follicles or significantly reduce follicle number. This significant reduction in ovarian reserve may cause immediate loss of fertility or early-onset infertility and menopause after cancer treatment.¹⁴ Younger women may be less susceptible to the reproductive impact of whole abdominal or pelvic radiation and prepubescent girls have an even better chance of achieving a healthy reproductive future after cancer treatment when compared with older women.^{15–16} Pelvic radiation can also permanently damage uterine elasticity and the musculature and vasculature of the endometrium, which may result in increased risk of miscarriage, mid-trimester pregnancy loss, preterm birth, and low birth weight regardless of the age of exposure.^{17–19} To this end, a study of childhood cancer survivors that received abdominal radiation indicated an increased risk for miscarriage and premature delivery later in life.²⁰

The neuroendocrine axis is critical to regulating the menstrual cycle and preparing the woman's body for pregnancy. The hypothalamus and pituitary glands are especially sensitive to high levels of cranial or brain irradiation, which may prevent regulated secretion of gonadotrophin-releasing hormone (GnRH), follicle-stimulating hormone, and luteinizing hormone, which in turn affects release of estradiol, progesterone, and prolactin. Spinal irradiation may also jeopardize reproduction after cancer, as higher rates of miscarriage have been reported after this treatment.²¹ Women whose cancer treatment causes damage to both the brain and pelvic regions are at the highest risk for reproductive loss after cancer. Thus, options for fertility preservation should be discussed early with patients who may receive total body irradiation. For example, women who undergo total body irradiation prior to hematopoietic stem cell transplantation should be informed of their fertility preservation options as early as possible.

Chemotherapy

Certain chemotherapeutic agents may also negatively impact future reproductive options for young cancer survivors. Chemotherapeutic treatments can be gonadotoxic to primordial follicles, as they cause DNA strand breaks, induce apoptosis, and reduce stromal function within the ovary.²² The most damaging chemotherapies include alkylating chemotherapies, such as cyclophosphamide, busulfan, melphalan procarbazine, and chemotherapeutic combinations that include alkylating chemotherapies. As found with radiation therapy, younger age appears to be fertoprotective for survivors, possibly due to the larger ovarian reserve present at the time of cancer treatment.¹⁵ While reduction of the ovarian

reserve is thought to be the cause of most of the reproductive damage from chemotherapy, there is also evidence that chemotherapy may impact the neuroendocrine axis. After receiving chemotherapy, many cancer survivors have growth hormone deficiency, hypothyroidism, or pubertal abnormalities.¹² Thus, chemotherapy may damage fertility by affecting either the nervous system or pelvic reproductive organs.

Many female survivors may have difficulty conceiving after cancer treatment, but the infertility risks for different age groups and cancer treatments are variable.²³ The risk of immediate and long-term amenorrhea after cancer treatment is impacted by both the specific chemotherapeutic regimen used and the age at which the woman was exposed.²⁴ In addition, women may experience transient chemotherapy-induced amenorrhea, with menstruation resuming after cessation of treatment. The type of chemotherapy, such as the inclusion or absence of alkylating agents, has a significant effect on menstruation recovery.^{25–26} In one study of breast cancer patients who were treated with cyclophosphamide, methotrexate, and 5-fluorouracil, no patient reported resumption of menses, while other treatments (e.g., doxorubicin and cyclophosphamide; doxorubicin, cyclophosphamide, and paclitaxel) resulted in increased rates of recovery.²⁶ Furthermore, while more than half of women with at least 6 months of amenorrhea do resume menstrual cycles within three years, only 10% of women who experience more than 24 months of amenorrhea are likely to resume menses. In addition, age at diagnosis is a significant predictor of amenorrhea. Women over the age of 40 years at the age of cancer treatment are 25 times more likely to have 6 or more months of amenorrhea than those treated at age 35. In contrast, only 11% of women 20–34 years of age reported to a loss of menstruation 6 months or more after the completion of chemotherapy.²⁶

Regardless of whether treatment-induced amenorrhea is transient or not, premature menopause is a significant concern for the reproductive and long-term endocrine health of cancer survivors. Studies of childhood cancer survivors indicate that premature menopause is most likely to occur in patients exposed to pelvic radiation or alkylating agents.²⁷ Ovarian failure in female survivors of pediatric cancer was found to be most common in those patients who received >10 Gy of radiation to the pelvis, alkylating agents, or procarbazine.²⁷ However, in studies where female cancer survivors received treatments without alkylating agents (e.g., doxorubicin, bleomycin, vinblastine, and dacarbazine; epirubicin, bleomycin, vinblastine, and prednisone) no significant increase in premature menopause was observed and patients did not experience subfertility.^{28–31} Though the data regarding the fertility of cancer survivors is far from complete, obstetricians, gynecologists, and family physicians may find models to predict premature menopause to be of some use, offering both providers and patients a general risk estimate after cancer treatment.^{16,32}

Surgery

Surgical procedures required to treat cancer may also affect the fertility of cancer survivors. For women diagnosed with gynecologic cancer, these procedures can include removal or one or both ovaries and partial or complete removal of the fallopian tubes, uterus, vagina, or cervix. Additionally,

procedures that affect the bladder, large intestine, and rectum may also impair a woman's ability to carry a pregnancy to term. As fertility and survivorship considerations have gained exposure in the clinical and public spheres, cancer treatments have been identified that provide women and girls with a greater chance at a reproductive future. Fertility-sparing procedures—for example, radical trachelectomy for early-stage cervical cancer—may increase the likelihood to conceive and carry a pregnancy after cancer.

Fertility Preservation Prior to Cancer Treatment

Historically, women have had few options to preserve their fertility when compared with men. In recent years, however, a number of fertility preservation techniques have been developed for females. Some of these methods have been adapted from those used in the assisted reproductive technology (ART) field, and others have been developed specifically to preserve the reproductive options for patients prior to undergoing cancer treatment. Current emphasis is being placed on the development of new fertility preservation options to provide a fertile future for all young cancer patients, including those who cannot participate in traditional ART treatments, such as prepubertal girls.^{33–34}

Embryo cryopreservation

Embryo cryopreservation following *in vitro* fertilization (IVF) is the most widely available and well-established fertility preservation strategy today.³⁵ According to the Society for Assisted Reproductive Technologies, data from 2010 indicate that 38% of frozen–thawed embryo transfers resulted in live births to women younger than 35 years (average 1.9 embryos transferred).³⁶ Embryo cryopreservation is a common fertility preservation option for women with partners or sperm donors who can contribute sperm for egg fertilization. However, the additional decision making required to select donor sperm may be an insurmountable barrier, emotionally and logistically, for some women in the immediate period after a cancer diagnosis. The ovarian hyperstimulation required for *in vivo* follicle development prior to retrieval may require a slight delay of cancer treatment, from 2 to 4 weeks; this delay may not be possible for women with certain cancers. Furthermore, ovarian stimulation can only be used in postpubertal women. In addition, patients must be physically evaluated and determined to be eligible to undergo ovarian stimulation. Thus, embryo cryopreservation may not be a suitable option for all female cancer patients. It is also important to counsel women that pregnancy rates for women undergoing embryo cryopreservation for fertility preservation are currently unknown.

Oocyte cryopreservation

Hormone-induced hyperstimulation can also be used in the absence of a sperm donor to recruit follicles for immediate oocyte cryopreservation. The large water content of mature eggs—the largest single cell in the mammalian body—has posed challenges to the freezing process. In the past decade, advances in a form of the rapid-freezing called vitrification has significantly improved mature egg cryopreservation and thaw rates for women who wish to preserve their fertility in the absence of donor sperm. Egg cryopreservation is an

option for postpubertal girls and women who do not have a partner and do not wish to use donor sperm. Oocyte cryopreservation is considered ethically preferable for legal minors, avoiding the need for the complex decision-making process required to choose donor sperm for embryo banking.³⁷ Historical success rates for egg cryopreservation had been low; however, with the advent of new vitrification processes, recent studies indicate that egg survival rates after thaw can be upwards of 90%.^{38–39} The American Society of Reproductive Medicine (ASRM) recently reversed older guidelines, stating that oocyte cryopreservation should no longer be considered experimental.^{40–41} With the increased success rates and the research on egg cryopreservation that has occurred in recent years, ASRM now identifies oocyte cryopreservation as an established technique for fertility preservation.^{42–43}

Ovarian tissue cryopreservation

An investigational technique, ovarian tissue cryopreservation may provide reproductive options to additional subsets of young cancer patients. This may be an option for females unable to undergo ovarian stimulation or prepubertal girls.^{44–45} For this to be accomplished, either an entire ovary or a portion of an ovary is removed, typically laparoscopically, and the cortex is cryopreserved. Patients need to be healthy enough to undergo surgery in order to have this procedure. According to the world literature, 37 children have been born from ovarian tissue transplantation; however, the total number of women who have attempted autotransplantation is not known, preventing accurate estimates for the success rate for this technique.^{46–50} Despite not knowing the total number of autotransplantations attempted, the success rate of this method can be inferred from data collected from several European centers that have reported the number of attempted autotransplantations in addition to live births at their respective centers. Between these four centers, 80 women attempted autotransplantation and the pregnancy rate was found to be 25% (20/80), with 16 women reporting a live birth.⁵⁰ Hormonal and reproductive results from published ovarian tissue transplantation procedures indicate that ovarian tissue may provide hormonal and reproductive capacity for a limited period of time.⁵¹ In addition to fertility preservation, recent research and patient cases indicate that ovarian transplantation may also be used to restore hormonal function in women with early onset menopause or to induce puberty in age-appropriate cancer survivors.^{52–53}

Ovarian tissue cryopreservation may not be an appropriate fertility preservation option for all cancer patients. With autotransplantation comes a potential risk of reintroducing cancer cells.^{54–55} Though the exact risk is unknown, autopsies of cancer patients show that cancer metastasis to the ovaries range from 8.4% to 55% depending on the type of cancer.⁵⁶ In one study, eight patients aged within the range of 13 and 20 years old with Ewing sarcoma (EWS), which recently has been reclassified from low to moderate risk of ovarian metastasis, were examined.^{55,57} Based on pathological/molecular studies, there was no evidence of EWS in the ovaries; however, in one patient a reverse transcription polymerase chain reaction (RT-PCR) showed EWS translocation despite the absence of pathological evidence.⁵⁷ Among pathologies investigated, leukemia presents the highest risk of reintroducing malignant

cells with autotransplantation, especially if ovarian tissue cryopreservation was performed when that patient had active disease. However, there is a much a lower risk of reintroducing malignant cells if ovarian cryopreservation is carried out when patients are in complete remission.⁵⁵ Thus, women with pelvic or hematologic cancers may not be appropriate candidates for ovarian tissue transplantation. Instead, researchers are working to perfect techniques of *in vitro* follicle growth from cryopreserved ovarian tissue.⁵⁸ The ability to grow follicles and mature eggs *in vitro* to a stage where they are capable of fertilization would allow women to preserve their fertility without a delay in cancer treatment and without the risk of reintroducing cancer cells.

Ovarian transposition/oophoropexy

A variety of other fertility preservation methods of established and experimental natures also exist that provide options for women with specific cancers or treatment types. Two standard fertility preservation techniques can be offered to women who would like to protect their reproductive organs from radiation therapy. Ovarian transposition/oophoropexy involves surgically moving the ovaries and fallopian tubes out of the field of radiation exposure, and radiation shielding further blocks radiation to the reproductive organs. However, neither of these techniques protects against the gonadotoxic effects of chemotherapeutics.⁵⁹ Furthermore, oophoropexy does not protect the uterus from radiation-induced structural and vascular damage that may reduce the likelihood of embryo implantation and impair a woman's ability to successfully carry a pregnancy to term.⁶⁰ In one study 37 cases of ovarian transposition were examined. Of this sample size, 18 pregnancies were achieved among 12 patients (32%). Five of these pregnancies ended in miscarriage and the other 13 pregnancies produced 15 live births.⁶¹

GnRH agonist treatment

Ovarian suppression to prevent iatrogenic loss of ovarian reserve, using a gonadotropin-releasing hormone agonist, is another potential method of fertility preservation being actively investigated. The precise mechanism of these drugs is unknown and the results of studies regarding the efficacy of GnRH agonist (GnRHa) for fertility preservation purposes are inconsistent.^{62–63} In a recent study that measured menopausal status of cancer patients who underwent chemotherapy with and without GnRHa, researchers found that a year after the last cycle of chemotherapy, premature menopause was significantly lower for women in the agonist group when compared with the control group.⁶⁴ While menstruation in these patients is not an indicator of current fertility or reduced ovarian reserve, it does provide evidence that GnRHa may be a potential way to maintain long-term endocrine health after cessation of cancer treatment.⁶⁵ More recent studies in women with breast cancer suggest that treatment with GnRHa may decrease the risk of premature ovarian failure.^{64,66} While GnRHa treatment has been associated with a statistically significant reduction in premature ovarian failure, additional work using more established markers of ovarian reserve is needed to better assess the role of GnRHa as a method for fertility preservation.^{67–68} In addition, studies comparing various GnRHa should be done. Furthermore, accurate communication to patients about the differences

between menstruation and fertility is essential. Although there is still controversy over GnRHa in preserving fertility as a standalone treatment, its administration as a co-treatment to cryopreservation of embryos, ova, and ovarian tissue may increase the odds of fertility preservation.⁶⁵

Assessing Ovarian Reserve

Before and after cancer treatment, female patients may wish to assess their fertility status. The gynecological community and family practitioners may aid cancer survivors during this challenging time by providing them with information about their ovarian reserve and ability to carry a pregnancy and reviewing reproductive options. While assessing any remaining endogenous reproductive ability in cancer survivors, clinicians should consider the patient's age at diagnosis and their current age, cumulative doses of chemotherapy and radiation, types of chemotherapies used, and the patient's menstrual and fertility history.

Assessing endogenous reproductive potential and ovarian reserve after cancer treatment can include a variety of measurements. Follicle stimulating hormone and estradiol blood measurements at day three of the menstrual cycle can indicate potential issues with ovarian health or the neuroendocrine axis. Currently, the most accurate hormonal measure of ovarian reserve can be achieved with anti-Müllerian hormone (AMH) testing. AMH stays relatively stable across the menstrual cycle compared with other hormonal measures and is constant throughout the reproductive lifespan before decreasing prior to menopause. For these reasons, it has been used as a measure of response to hormonal stimulation for traditional infertility patients undergoing IVF.⁶⁹ In conjunction with AMH testing, transvaginal ultrasounds to count antral follicles can provide an indication of the number of dormant and growing follicles within a woman's ovaries. As more women delay childbearing into their thirties, more will face a cancer diagnosis prior to having biological children. As such, many cancer survivors will have an interest in discussing their future reproduction with their primary care physicians while still in some state of active cancer treatment or during survivorship.

Timing of Pregnancy

Considerations about the safety and timing of pregnancy after cancer should be discussed among patients, their cancer treatment team, and their family physicians. Women who are not interested in pregnancy should be encouraged to use adequate contraception. Multiple retrospective cohort studies have found no increased risk of cancer recurrence in breast cancer survivors who become pregnant.^{70–71} In fact, retrospective studies demonstrate that breast cancer survivors who become pregnant after diagnosis had improved survival compared with those who do not become pregnant.^{70–71} Yet, while robust, these retrospective studies are limited by inherent bias issues and must be viewed accordingly. Though questions about when to attempt pregnancy after cancer treatment are common, limited data exists to guide the field. One study in breast cancer survivors found a survival benefit in women who waited 2 years or more after diagnosis to attempt conception.⁷¹ In cases where the oncology team suggests a 5- to 10-year wait before attempting pregnancy, age can be an important factor. Five to ten years of the

selective estrogen receptor modulator (SERM) treatment tamoxifen will impact a 25-year-old differently than a 35-year-old. Women who are taking SERMs are able to ovulate and thus should be on adequate contraception during treatment as tamoxifen is a teratogen. If interested in conception during this prescribed treatment, women should discuss how to best incorporate pregnancy into their survivorship plan; for example, by discontinuing treatment during a pregnancy and then reinitiating after childbirth. Such factors should be discussed in detail before, during, and after cancer treatment.

Other Family Building Options

Though cancer treatment can significantly impact a woman's ability to conceive and carry a pregnancy to term, many options are now available to cancer survivors. Women who have a reduced ovarian reserve but are able to carry a child may utilize a donor eggs fertilized with a partner's semen or donor sperm. Using a donated embryo may also be of interest to some women. Alternatively, women with a healthy ovarian reserve who are unable to successfully carry a pregnancy due to surgical or radiation damage to the reproductive organs may undergo hormonal stimulation and IVF with the resulting embryos carried by a gestational surrogate. Adoption is also an option for cancer survivors, though recent research examining policies of adoption agencies revealed isolated cases of *de facto* discrimination.⁷² However, significant variability exists in the attitudes of the adoption community, and survivors should be encouraged to work with multiple agencies.

Conclusion

More than 40 years ago, the "war on cancer" was launched with the passage of the National Cancer Act and the strengthening of the National Cancer Institute. At that time, a cancer diagnosis was often a death sentence. Since then, survival rates for cancer patients have increased dramatically, raising the importance of survivorship and overall quality-of-life considerations for the many people who successfully fight their disease. As 10% of all cancer patients are under the age of 40 at diagnosis, these considerations often include the desire to have a family after cancer and long-term endocrine management that can affect the overall health of survivors. Though the number of fertility preservation options for women has increased significantly in recent years, many young cancer patients still do not receive information about the ability to preserve their fertility prior to cancer treatment and reproductive counseling after treatment.^{73–74}

The primary care community is in a unique position to provide this information, including referrals to appropriate subspecialists and care for young female cancer survivors, incorporating reproductive goals into the patient's overall survivorship plan. We recommend early referral to either a reproductive endocrinology and infertility specialist or a gynecologist comfortable with discussing fertility preservation options.

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