Chapter 14

Childhood Cancer: Fertility and Psychosocial Implications
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Having your child diagnosed with cancer is one of the most trying experiences a parent can endure. Greater than 15,000 children and adolescents under the age of 19 are diagnosed with childhood cancer each year in the United States [1]. Childhood cancer is comprised of a wide spectrum of malignancies, and outcomes are dependent upon histology type, disease origin and site, race, sex, and age at diagnosis [2]. Fortunately, advances in treatment and supportive care have led to a significant increase in survival rates for childhood cancer patients. Ries et al. reported that from 1950 to 1954 the 5-year survival rate was 20 % for children diagnosed with cancer between the ages 0–14 years [3]. Almost 50 years later, by 1995–2000, the 5-year survival rate rose to 80.1%, and in the past 25 years alone this rate increased by 20 % for children ages 0–19 years [4].

Approximately 270,000 Americans are childhood cancer survivors and, by 2010, an estimated 1 in every 250 adults will be living with a history of childhood cancer [5,6]. Recent studies demonstrate that while more childhood cancer patients are surviving, a high percentage of survivors are encountering serious “late effects” from their therapy. These late effects include, but are not limited to, cardiac, pulmonary and endocrine disorders, increased morbidity and mortality, as well as moderately to severely affected status in one or more of the primary domains of health (i.e., general health, mental health, functional status, limitations in activity, fear, or anxiety) [7,8]. This chapter will not go into detail on the myriad of late effects of childhood cancer treatment. Rather, we will focus on the fertility effects that adult survivors of childhood cancer may experience, including the emotional consequences of living with threatened or impaired fertility. Finally, some of the barriers to ongoing follow-up medical care will also be addressed.

Recent Research on Late Effects and Infertility

In 2006, Oeffinger et al. published data from the Childhood Cancer Survivor Study (CCSS) that investigated the health status of adult survivors of childhood cancer. The study determined the incidence and severity of chronic health conditions in adult survivors as compared with their siblings [9]. The CCSS was established in 1994 as a resource to examine the long-term outcomes of a cohort of 5-year survivors of pediatric and adolescent cancer who were diagnosed between 1970 and 1986. The CCSS consists of more than 14,000 active participants from 26 institutions in North America, including survivors of leukemia, brain tumors, Hodgkin’s disease, non-Hodgkin’s lymphoma, Wilm’s tumor, neuroblastoma, soft-tissue sarcoma, and bone tumors. All participants provided self-reported socio-demographic and healthrelated information. The vast majority of the CCSS cohort is now in the second and third decades of their lives, and many years past their diagnosis of childhood cancer. The results of the research conducted from this
cohort of survivors have been extremely valuable to health care professionals and survivors alike.

Based on data from the CCSS, the survivor population is at an increased risk for a broad spectrum of adverse outcomes such as early mortality, second cancers, pulmonary complications, pregnancy loss, and giving birth to offspring with low birth weights [10]. Oeffinger’s compelling study consisted of 10,397 survivors who were a mean age of 26.6 years at the time of the study and an average of 17.5 years had lapsed between their cancer diagnosis and their participation in the study. The survivors’ siblings (n = 3,034) served as the study’s control group, who had a mean age of 29.2 years. Oeffinger et al. found that 62.3% of adult survivors had at least one chronic condition (grade 1–4) and 27.5% had a severe, disabling, or life-threatening condition (grades 3 or 4) on the Common Terminology Criteria for Adverse Events Scale. Furthermore, survivors were 8.2 times as likely to have a grade 3 or 4 condition as their siblings. The study also noted that female survivors reported a 3.5 (2.7–5.2) relative risk (RR, 95% CI) of ovarian failure vs. their siblings. Ovarian failure was the second most common reported grade 3 or 4 condition out of ten conditions. Among female survivors, 2.79% reported ovarian failure compared with 0.99% of their siblings [9].

Predicting the risk of ovarian failure or azoospermia among childhood cancer survivors can be complicated. Fertility outcomes in childhood cancer depend on multiple interacting factors, namely the type of chemotherapy agents given to the patient, the site where radiation was administered, and the age of the patient at the time of treatment [11] (also see Gracia and Ginsburg, this volume). As one of the pioneer researchers in fertility effects after childhood cancer, Byrne described the incidence of infertility among childhood cancer survivors through the findings of the National Cancer Institute’s Five Center Study. This study was one of the first investigations to research fertility outcomes and the health of offspring in survivors of childhood cancer by using a large cohort of patients. The study’s participants were diagnosed with pediatric cancer between 1945 and 1975. Out of 1,232 married survivors of childhood cancer, there was a 15% fertility deficit among survivors. The overall treatment effects were more severe in men, who had a 15% decrease compared with a 7% decrease in female survivors. Men were more susceptible to alkylating agents such as cyclophosphamide and had less than one-half the fertility of their brothers, who served as controls. Women showed no fertility deficits following treatment with similar agents. Conversely, radiation affected both sexes similarly, with greater fertility reductions if the patient was treated below the diaphragm.

Although azoospermia and ovarian failure are the most extreme fertility threats to cancer survivors, there are also less severe but equally serious problems that survivors may encounter. For women, Byrne’s study considered the risk of premature menopause, which is a risk for young women who received alkylating agents and/or abdominal radiation. With premature menopause, survivors may resume their menses after treatment and retain their fertility for several years without any overt indications of pending problems. Byrne’s 1999 study provided the first data on this important complication and found that the principal risk factors for early menopause after cancer were treatment after the onset of puberty, treatment with radiation below the diaphragm, and the use of alkylating agents. Byrne found that survivors were twice as likely (RR = 2.32, p < 0.01) as their control siblings to reach menopause during their twenties. However, there was no excess risk during their thirties (RR = 0.78). Survivors diagnosed after
puberty and treated with radiation below the diaphragm were nearly ten times more likely to reach menopause during their twenties than controls, regardless of their primary diagnosis. The RR was 9.6 for Hodgkin’s disease survivors and 8.56 for all other cancers [11].

Despite the fertility issues that survivors face, most childhood cancer survivors will go on to produce healthy, live offspring [12–14]. However, studies have indicated that survivors worry about their own reproductive abilities and the health of their offspring [13,15]. Although the majority of survivors will be able to have their own children, infertility is a reality for many childhood cancer survivors. The exact number of survivors affected is unknown, but infertility is one of the most common chronic medical problems reported by childhood cancer survivors and can be a primary concern, particularly among female survivors [16,17].

**Addressing the Threat of Infertility**

Is the price of infertility a necessary price to pay for survival? In past decades, one would argue yes for female patients, as they lacked viable options to preserve their fertility. Sexually mature men have long had the option to cryopreserve sperm before beginning fertility-threatening cancer treatment. Without alternatives for female patients, infertility can be a considerable cost to pay; some survivors describe the loss of fertility as painful as facing cancer itself [18,19]. Recent advances in fertility preservation may soon offer potential methods for females of all ages to protect their reproductive capacity from damaging radiation and/or chemotherapy [20] (see Min, Woodruff, and Shea, this volume). Current literature focuses on the further development of preservation techniques and the numerous ethical and legal questions (see Zoloth and Backhus, this volume), but little knowledge is available on the attitudes and opinions of childhood cancer survivors and their parents regarding fertility preservation. As basic science research begins to enter the clinical arena, a large number of unanswered questions remain regarding the application of the procedures, the legal and ethical considerations involved, and the receptiveness of patients and their families to fertility preservation questions that are only recently beginning to be addressed.

Additional questions surrounding communication and decision making at the time of diagnosis are also important given that decisions about fertility preservation must be made before treatment begins. Parents, physicians, and patients are required to make a complex decision in a short amount of time during an extremely stressful situation, similar to the anxiety involved in the informed consent process of clinical cancer research trials [21]. In order for fertility preservation to become a realistic and valued addition to the treatment of childhood cancer patients, a better understanding of the decision-making process that parents and their children go through at the time of diagnosis and their interest in fertility preservation is needed (see Clayman, Galvin, and Arntson, this volume). Further, a more thorough exploration of patients’ and parents’ thoughts regarding the child’s fertility at the time of diagnosis and later in life will be valuable in the continued advancement and eventual application of fertility preservation.

**Childhood Cancer Survivors and Fertility Preservation**

There are several ongoing studies that are beginning to address the perspective of survivors themselves, which will be a critical component to delivering fertility preservation in the clinic.
One such study, based out of Northwestern University, was a qualitative exploratory study that consisted of four focus groups: two with adult women who were diagnosed and treated for cancer as adolescents and two with their parents (for more details, see Nieman et al., this volume). The purpose of the study was to explore and compare the attitudes towards fertility and fertility preservation among and between the survivors and parents. Eligibility criteria for survivors included diagnosis and treatment for childhood cancer between the ages of 13 and 21, English-speaking, and willingness to participate in a tape-recorded focus group. The eligibility criteria for parents of survivors included they be English-speaking and willing to participate in a tape-recorded focus group. Survivors were recruited from the Survivors Taking Action & Responsibility (STAR) Program at the Robert H. Lurie Comprehensive Cancer Center of Northwestern University in Chicago, IL, and were eligible to participate with or without a corresponding parent. Adult survivors enrolled in the study were either in ovarian failure or were at risk for infertility due to the treatment they received for their childhood malignancy. Topics addressed in the moderators’ guides included (1) short- and long-term concerns at the time of cancer diagnosis, (2) attitudes about fertility at the time of diagnosis and presently, and (3) reactions to a proposed clinical research study in ovarian tissue preservation. For the third topic, participants were asked to read an educational brochure on a proposed clinical research study in ovarian tissue cryopreservation that explained the purpose of the study and the procedures involved, including laparoscopic surgery to remove an ovary.

In the first set of focus groups, four survivors and three parents participated, and in the second set, held two days later, six survivors and seven parents participated. The median age of the ten survivors was 26 years with a range of 23–36 years. Median age of survivors at the time of diagnosis was 14.5 years with a range of 13–21 years. Nine of the ten survivors were diagnosed with Hodgkin’s disease and one with Ewing’s sarcoma. Eight of the ten survivors received chemotherapy and all received radiation (see Nieman et al., this volume).

This study highlighted that at the time of diagnosis, most survivors reported that fertility was not an issue they considered important. However, when survivors were told that their ability to have their own children was going to be threatened, fertility gained in importance for many of them (see Nieman et al., this volume). In contrast to the time of diagnosis, survivors discussed how fertility has become a relevant issue in their lives, particularly as peers marry and have children and questions about career vs. family arise in their own lives. For many, fertility was something they took for granted until learning about the possible late effects of their treatment.

As fertility becomes an increasingly salient issue for survivors as they age, uncertainty about their fertility status remains for many. Half of the survivors in this study and other studies were unaware of their present fertility status [15,22]. At the time of diagnosis, survivors and their parents were focused on survival. Few parents remember talking with physicians about fertility at the time of diagnosis. For the majority, fertility became an issue after treatment. One parent said, “…I wasn’t thinking about fertility issues. That was a horror that was held for later.”

With this mindset, survivors and parents were overall very receptive to learning more about the proposed fertility preservation research study. Survivors and parents agreed that infertility was not of utmost concern at the time of diagnosis and that diagnosis and treatment can be an overwhelming time period. Despite these concerns, both survivors and parents agreed that
fertility preservation was something they would have considered and would at least have liked to be presented with as an option. Parents and survivors said that the research study would have given them hope that there is life beyond cancer. Participants also recognized how meaningful it is to have reproductive choices, something that male patients have with sperm banking. Many parents commented that they wished they had had something like this available to their daughters. This level of interest among survivors and parents in a research study on fertility preservation, which does not necessarily guarantee a reproductive option, underlines the importance of reproductive choices for cancer survivors and the great relevance of fertility. When asked about extending the program to younger children, survivors and parents felt that fertility preservation is an option that should be presented to everyone, regardless of age. Adolescent cancer patients and their parents echo this interest in fertility preservation. Burns et al. conducted a survey-based study of female cancer patients with a mean age of 15.5 years and their parents. The study found that patients and parents were interested in research treatments to preserve fertility, but were unwilling to delay treatment for such efforts [23].

In order for a possible late effect like infertility to be effectively addressed through fertility preservation, options must be incorporated into cancer care beginning from the diagnosis stage. Advancements should continue to be developed in the area of reproductive technologies, but health care personnel must be prepared to communicate professionally about fertility-related treatment effects with patients and their families and take a proactive and farsighted approach to comprehensive cancer care (see Nieman et al., this volume).

**Male Infertility**

The majority of this chapter has been focused on female adult survivors of childhood cancer. Despite this focus, many male adult survivors of childhood cancer are deemed sterile, a no less devastating late effect than female infertility, and many male survivors are at an increased risk for infertility (see also Gracia and Ginsburg, this volume and Brannigan, this volume). However, there have been much greater strides forward in addressing male infertility than with female infertility, specifically with the latest advances in in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI) [24]. Building on these advances, research in the field of childhood cancer patients continues to address the issue of male infertility.

Kenney and colleagues studied gonadal function in 17 adult male survivors of childhood sarcomas who were treated with high dose pulse cyclophosphamide as part of a combination drug regimen. Of the 17 patients who underwent semen analysis, 58.8% (10) had azoospermia and 29.4% (5) had oligospermia, while only 11.8% (2) had a normal sperm count. The two survivors with a normal sperm count had received the lowest cumulative doses of cyclophosphamide, < 7.5 mg/m2. The chemotherapeutic exposure prior to puberty was not found to be protective for sterility and the risk of infertility increased with the higher doses of therapy [25].

Byrne et al. revealed more reassuring results from a large study of male long-term survivors of acute lymphocytic leukemia (ALL) (n = 213) diagnosed during childhood or adolescence. Younger males, specifically those under 10 years of age, treated with cranial but not spinal radiation were less likely to become fathers than the control group. The male survivors’ relative
fertility was only 9% (95% CI 0.01–0.82) of the control group fertility. Byrne and her colleagues also revealed that male survivors had more concerns than study controls \((n = 145)\) on a number of factors related to family planning and male health conditions. One-third had been told that they might have trouble having children and many were concerned with their own health and the health of their children [26]. In the clinical setting, the assessment of male infertility is done through semen analysis. Once a young adult male survivor is ready to learn his fertility status, the health care professional can direct him to an andrology lab for testing. The results need to be discussed in a planned and private discussion, especially if results reveal azoospermia or oligospermia. The health care professional must be prepared to counsel the patient and/or their partner on reproductive technologies available to them.

**Access to Care**

Currently, adult survivors of childhood cancer are being studied by numerous investigators and results are being disseminated through the Internet, journals, and at medical and nursing conferences. Regardless of this growth in the field of survivorship, adult survivors are struggling to find appropriate long-term follow-up medical care. The difficulty lies in finding generalists and specialists who understand the type of therapy the survivors received and the actual or potential late effects that may arise from these treatments. Most family practice physicians or internists care for a few cancer survivors in their practice and becoming an “expert” is an unrealistic expectation. In general, we have learned that survivors themselves are not knowledgeable about the late effects of their cancer therapy [27]. This introduces an additional difficulty in dealing with this population of patients. Survivors lack knowledge about the current recommendation that they should receive systematic long-term follow-up care on a regular basis for the rest of their lives [28].

To fill this need for adult survivors, various models of care have been addressed in the literature. For example, current models include approaches like community-based programs and actual transition programs for adults to move into after “graduation” from the pediatric medical setting. Regardless of the model, the goal of each approach remains the same. By educating and empowering survivors, the hope is that they will become their own advocates, assume follow-up responsibilities, and gain access to the specialized care they need [29]. Such follow-up care is necessary to treat actual late effects like early osteopenia that can accompany ovarian failure or cardiomyopathy from treatment with anthracyclines. There is also a need to screen appropriately for other delayed effects that may take decades to present, such as secondary malignancies or coronary artery disease. Survivors and their physicians must also learn about new resources available to them, such as the Children’s Oncology Group (COG). Guidelines regarding long-term follow-up care and links to health topics for survivors of childhood, adolescent and young adult cancers are available at http://www.survivorshipguidelines.org [30].

Although childhood cancer survivors face numerous late effects, results have consistently shown that the majority of adult survivors of childhood cancer are faring well in terms of adjustment, emotional state, and moving on with their lives [31,32]. However, survivors of pediatric brain tumors are not managing as well. Zebrack et al. demonstrated that pediatric brain tumor survivors have higher levels of global distress and higher depression scores, which are believed to be related to difficulties in becoming re-integrated into society, such as attaining a job and
getting married after treatment [33]. Additionally, a study by Rourke et al. found that Post Traumatic Stress Disorder (PTSD) affects a subset (nearly 16%) of young adult survivors of childhood cancer. Post Traumatic Stress Symptoms (PTSS) include re-experiencing the trauma (e.g., flashbacks and nightmares), avoidance of reminders of the trauma, emotional numbing, general anxiety, and physiological arousal. Survivors with PTSS and PTSD may be less likely to follow up with medical personnel due to the distress it causes them [34]. Given the combination of physical and psychological sequelae that may afflict adult survivors of childhood cancer, the need for long-term follow-up care is great, not only for reproductive matters but also to ensure that survivors live as healthy and full lives as possible.

Conclusion

After battling pediatric cancer, many survivors endure numerous difficulties throughout their lives despite being cured of their disease. Fertility deficits are only one of the problems that they face, but the effects of being infertile or sterile can be devastating. The uncertainties of infertility and sterility do not diminish as survivors move into adulthood, rather, they shift focus. As female survivors mature into young adults, issues such as fertility status become pressing. For males, the reality of being sterile as a survivor can be difficult to accept once family planning begins. The risk and experience of infertility and sterility is closely connected to a survivor’s identity, intimate relationships, plans for a family, and their concerns regarding their future and happiness. Infertility and sterility is far from a singular experience.

Connecting the pieces that make up a survivor’s experience with infertility will help identify unanswered questions and, more importantly, provide guidance for clinical practice and future research. Health care professionals must now incorporate strategies to assist young adult survivors with family planning options and reproductive technologies if applicable. Since adult survivors of childhood cancer appear to lack critical information about their fertility status, efforts need to be made to equip survivors in making informed choices about family planning. A comprehensive fertility assessment of the survivor should not only include laboratory work and a health history but also consider their knowledge of their reproductive abilities as well as childbearing aspirations. Health education related to birth control practices and options and sexual behavior are an important part of a follow-up visit. Clinicians must become aware of support agencies such as Fertile Hope (http://www.fertilehope.org), Planet Cancer (http://www.planetcancer.org), and the Lance Armstrong Foundation (http://www.laf.org), which can offer important information on reproductive options and help address the psychosocial needs of survivors [15]. Although the field of oncofertility is young and growing, resources and an increasing number of options already exist. Informed, dedicated clinicians in concert with educated, empowered survivors can continue to improve the quality of life and health for childhood cancer survivors.

References


