

Assessing the Reproductive Concerns of Children and Adolescents with Cancer: Challenges and Potential Solutions

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Infertility is often an expected side effect of cancer treatment, although the idea of fertility and sterility may be difficult for the child or adolescent patient to comprehend. Several established fertility preservation options exist for males and females, such as cryopreservation of sperm or embryos. Experimental therapies, which require institutional review board approval, are also being tested. While the science of fertility preservation for adolescents with cancer is advancing, the social science research in this area is lacking. Specifically, there are only a small number of studies about the psychological reproductive concerns in the pediatric oncology population. These studies have provided groundbreaking information for future research, but also illustrate the challenges in conducting research in this area. This article comments on those challenges and, when possible, presents solutions for confronting them.

Introduction

CANCER WAS ONCE a predominately fatal diagnosis for children and adolescents. Yet advances in treatment, screening, and early diagnosis over the past 40 years have dramatically improved rates of childhood cancer survival. In its most recent report on cancer, the U.S. Centers for Disease Control and Prevention estimated that 16.5 children and adolescents per 100,000 were found to have cancer in 2000.^{1,2} Cancer continues to be a leading cause of death for children and adolescents in the United States, although the number of children who survive cancer continues to increase. Over the past 30 years, the 5-year childhood cancer survival rates have increased from 58% to 79.6%.³

As the population of survivors continues to grow, there is great need to develop quality care along the survivorship trajectory. While survival is the ultimate goal of treatment, this often comes with side effects that the patient may or may not be expecting. Side effects can be acute, chronic, and long-term and are often called "late effects." Physical late effects are caused by damage to healthy cells within the course of treatment that prevents these cells from normal development. Psychosocial late effects may impact emotional, social, educational, and economic functioning. The risk of developing late effects depends on cancer site, age at diagnosis, dosage of chemotherapy or radiation, area of the body treated, and genetic factors.⁴

Infertility (the reduced or lost capability to conceive a child) and even sterility (the inviability of sperm or eggs) are other potential side effects of cancer treatment. The exact risk of sterility or infertility from chemotherapy or radiation is unknown and not well studied in pediatric populations. This lack of information is especially true for prepubescent children. In adults, however, it is known that the rates and risk vary depending on age, gender, treatment received, site, and stage at diagnosis.⁵⁻⁷ Few studies have focused on the associations between treatment modalities and dose-response in relation to infertility in pediatric cancer survivors.⁸

Studies suggest that between 40% and 80% of adult female cancer patients are at risk of becoming infertile and between one-third and three-quarters of male cancer patients may become sterile after treatment for cancer.^{9,10} There are a variety of options available before initiation of cancer treatment to preserve or maintain a patient's fertility. Established options include sperm and embryo freezing and oophoropexy or repositioning the ovary out of the radiation field.⁷ Experimental options include cryopreservation of testicular tissue for prepubertal males and ovarian or oocyte cryopreservation for females. Sperm cryopreservation has been documented to have a 36% success rate with intrauterine insemination and a 50% pregnancy rate with *in vitro* fertilization and intracytoplasmic sperm injection.¹¹ For females, embryo cryopreservation can yield pregnancy rates of 60%, whereas

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ovarian transposition has success rates reported between 16% and 90% depending on age, dose, receipt of concomitant chemotherapy, and whether intracavitary brachytherapy or pelvic external beam irradiation was used.^{12–15}

Given the risk that cancer treatment may decrease fertility or even result in sterility for some pediatric cancer patients, it is critical that patients and their parents are informed and their concerns are addressed. The American Society for Clinical Oncology (ASCO) and the American Society for Reproductive Medicine formally recommend that physicians discuss the risks of infertility with all cancer patients of reproductive age.^{6,16} In 2008, the American Academy of Pediatrics developed their own guidelines suggesting that information about possible fertility preservation should be provided to children and adolescents, and referrals should be made to reproductive specialists when appropriate.¹⁷

Although the guidelines call for discussion about fertility loss with all patients of childbearing age, studies of adult cancer survivors suggest that less than one-half recall receiving information about fertility preservation from their providers.¹⁸ Moreover, adult cancer survivors suggest that failure to receive information about fertility preservation or to explore various issues that may emerge after receiving this information has been associated with regret and distress.¹⁹

Fewer studies have been conducted with adolescents to understand their concerns about potential fertility loss. Oosterhuis *et al.* surveyed 37 pediatric cancer survivors over the age of 14 and 97 parents and found that both patients and their parents were concerned about fertility, regardless of the treatment regime.²⁰ A Burns *et al.* survey of 39 patients with pediatric cancer aged 10–21 who were receiving or had completed treatment and their parents found that while patients were interested in learning about fertility preservation options, many were not willing to postpone treatment.²¹ Zebrack *et al.* found that 59% of 32 young adolescent cancer survivors reported they were unsure about their fertility status and had difficulty remembering their providers discussing these issues.¹⁸

Two qualitative studies explored fertility issues of adolescents with cancer. Chapple *et al.* found that males aged 16–26 were concerned about potential fertility losses, but faced several barriers to engaging in related conversations, including embarrassment and feelings of pressure to start treatment.¹⁹ This parallels the results of a 2006 study wherein the majority of 38 adolescents with cancer had a strong desire to know how their fertility was impacted by treatment, but no participants had utilized fertility preservation options due to the uncomfortable nature of discussing sex with healthcare providers while parents are present.²²

Although these studies provide valuable insights, they are primarily retrospective and potentially suffer from recall bias. In a rare prospective study, Anderson and colleagues asked pediatric oncologists to complete a form documenting fertility discussions with their patients.²³ Charts were reviewed for 1,030 patients to determine if discussion or referral related to fertility had occurred. For 63% of the patients, discussions about fertility occurred, primarily with males and those patients whom the oncologist believed were at moderate or high risk for infertility. Only 1% of females were referred to a reproductive specialist.²³

Understanding the reproductive concerns of adolescents with cancer is important in providing comprehensive cancer care. Nurses, social workers, and physicians who are better

able to assess the reproductive concerns of adolescents with cancer are better able to dispel myths, provide comprehensive information, and tailor these conversations and interventions toward each patient and family. Ability to assess and address concerns could result in improved decision making, patient-family-provider partnerships, and overall satisfaction with the quality of care. Researchers would also benefit from being able to better prospectively assess reproductive concerns of adolescents, as this would allow for exploring the associations between reproductive concerns and other outcomes, such as health-related quality of life, across the continuum of cancer care. As described previously, a few informative and insightful studies exist, but they also highlight the challenges in assessing the reproductive concerns of adolescents with cancer. These challenges, as well as recommendations for addressing them, are described below.

Challenges and Potential Solutions

How to assess concerns

When assessing the reproductive concerns of children and adolescents with cancer, researchers and clinicians are faced with choosing either an existing survey instrument or developing one themselves. The majority of existing scales measure the reproductive concerns of adult women with polycystic ovary syndrome or adult cervical cancer survivors.²⁴ Individual research teams have had to develop unique study instruments to assess the reproductive concerns of children and adolescents with cancer.^{20,25–27} To our knowledge, none of these instruments have been formally tested. This serves as a potential solution to accurately assess reproductive concerns. Determining the validity of instruments is important to ensure that a scale is measuring its intended constructs, that it correlates well with known groups, and that the results are reliable and replicable. A battery of psychometric tests should be performed to establish validity and reliability. Even if the instrument has been validated, systematic cognitive debriefing, in addition to pilot testing, should be conducted with any instrument that is used with adolescents with cancer. Systematic cognitive debriefing, in which adolescents are administered the instrument and afterward asked to assess the questions, should occur until saturation is reached.

New instrument development is another potential solution to assessing the reproductive concerns of adolescents with cancer. However, instrument development is a time- and resource-intensive process that must be done with scientific rigor. There is sufficient evidence in the literature that the first step in this process has been completed—the use of qualitative methods to provide content for item development.^{19,22,28} However, it is unclear if item banks have been created. Perhaps the lack of rigorous instrument development is due to a lack of adequate sample sizes needed to develop and test large item banks and to reduce those item banks by culling out items that do not show significance or relevance to the majority. Oftentimes it is difficult to recruit large pools of children and adolescents with cancer or survivors for these research projects. Further, there must be consideration regarding age-specific delineations, as well as recognition of differences in perceptions held by females compared to males regarding fertility concerns. Cooperative groups such as the Oncofertility Consortium or Children's Oncology Group might be a way to successfully conduct this research.

Variation in study sample

Development, testing, and validation become even more important when one considers the variation in study samples in this area of research. Fertility and reproduction should be addressed along the cancer continuum, from the point of diagnosis through survivorship when survivors may wish to have a child of their own (Fig. 1). Yet the reproductive concerns of adolescents with cancer may vary across that continuum and existing studies have not carefully partitioned the study samples. For example, in the Burns and Oosterhuis studies the authors did not indicate how many of the adolescents were recently diagnosed, in the midst of acute treatment, or were post-active treatment.^{20,21} Burns' sample is described as "receiving treatment, or had received treatment," and for the Oosterhuis study patients were ineligible if they "presented for a visit other than routine therapy or follow-up evaluation." Chapple's sample is described as male cancer patients aged 16–26 that had either completed or were still in active treatment.¹⁹ This presents a paradox in which reproductive concerns may become more relevant for a survivors as they finish treatment and experience the survivorship phase; however, the ideal time to preserve fertility is before treatment begins. By mixing study samples with a variety of adolescents in different phases of the cancer continuum, it is difficult to disentangle their true reproductive concerns and how these might be addressed. Longitudinal studies could follow adolescents across their cancer trajectories, assessing their reproductive concerns by cancer type, treatment stage, and developmental stage, and eventually assessing the concerns faced in each phase.

Appropriate language and cognitive functioning

When selecting or developing an instrument, it is important to ensure that study participants understand the questions being asked of them. This may be additionally challenging when developing an instrument for adolescents because the language used must be age-appropriate. Simply adapting a scale that was developed and validated for adults is not sufficient. Cognitive debriefing or focus groups can be used to evaluate the phrasing, individual words, and overall under-

standing of the questions. Sudman and Bradburn's book provides guidance for constructing study instruments with items that are brief and simple; free of questions that are embarrassing, not applicable, or have double negatives; clearly indicate differences between similar questions; and use equal numbers of positive and negative statements.²⁹ During the pretesting phase of instrument development, adolescents should be asked to explain what the questions mean to them, suggest substitute wording if needed, and identify poorly worded items. Likewise, response categories must be easily understood. Some adolescents may have difficulty distinguishing between responses such as "never," "sometimes," "rarely," "often," or "always." Time-dependent questions, which ask the adolescent to compare their current experiences with those in the past (such as before the cancer diagnosis), may also be problematic.

These issues are likely further complicated for adolescents who have decreased cognitive functioning as a result of treatment, such as those with central nervous system (CNS) tumors who received cranial radiation. Armstrong found that CNS survivors are at significant risk for development of adverse neurological health conditions.³⁰ Other studies have shown that compared to non-CNS survivors, CNS survival is associated with lower educational outcomes and incidences of employment.³¹ Because the brain continues to mature well into the mid-20s, cancer treatment administered during these developing years may impair cognitive functioning. Neuroscience studies also suggest that judgment and responsibility do not reach peak levels until age 19.³² Currently, no information exists about how cognitive development, or the interruption of this development due to treatment for cancer, might affect concerns about reproduction, ability or desire to participate in decision-making about reproductive choices, or how to measure these concerns when cognitive functioning has been affected by treatment.

Emotional reaction

Gauging the emotional reaction of children and adolescents to survey questions is also challenging and depends on the patient's present phase in the cancer continuum. Adolescents

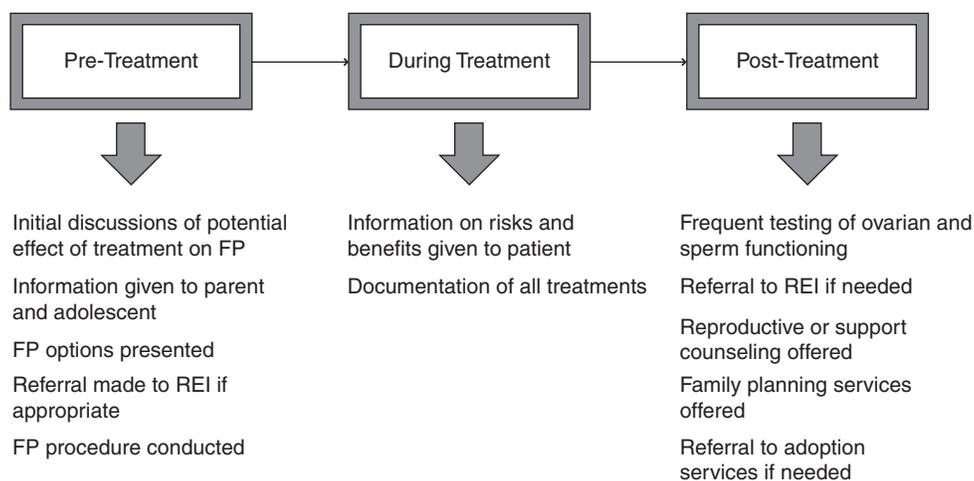


FIG. 1. Reproductive concerns across the cancer continuum. FP, fertility preservation; REI, reproductive endocrinology and infertility.

may have strong negative reactions to questions about fertility because (1) they were not given—or do not recall being given—information by their providers; (2) they are overwhelmed by their diagnosis; (3) their potential loss of fertility is hard to accept; or (4) their parents have not talked with them about reproduction or fertility and they have limited knowledge of human reproduction. Ethical dilemmas may arise when conducting this research. It can be reasonably expected that adolescents newly found to have cancer will be overwhelmed and upset, among many other emotions, and asking survey questions about fertility may provoke tears or discomfort. This may not necessarily be an adverse event related to the questions about fertility, but instead a reaction driven by their overall circumstances. Researchers must be sensitive to these reactions and prepared to handle them.

Distinct emotional reactions are most often dependent on the patient's point in the cancer trajectory. Studies that intermingle stages of illness and do not separate results by stage of illness will fail to account for this in their analyses and implications. Adolescents newly found to have cancer may have strong, negative emotional reactions when asked questions about fertility preservation, regardless of age or gender. However, it is unclear when and if those reactions are tempered. Research that stratifies samples by point on the cancer trajectory may conclude that adolescents with newly diagnosed cancer, or still in acute treatment, may be unable to have a reproductive concerns instrument administered to them without assistance from a member of the professional healthcare team. Social workers, pediatric oncology nurses, or child life specialists with specific training may be necessary to administer these questionnaires. At the very least, face-to-face administration is preferred over all other types of administration for adolescents with newly diagnosed cancer.

Parents may also have strong emotional reactions about their children and adolescents answering these types of questions or being asked the questions themselves. It is important to consider how a parent's negative reaction might interfere with the informed consent process, meaning that parents may not allow their child to be approached. Parental reaction might affect their present and future discussions with their child about fertility and reproduction.

Parental concerns

Parents are the legal decision makers for adolescents with cancer. Although most healthcare providers advocate that adolescents should be given all pertinent information and triadic decision making should occur, final decisions are left to the parents or legal guardians. The Internet might be an especially effective venue to provide adolescents with information. Assessing the reproductive concerns of adolescents with cancer requires the permission of the parent, and some parents may not be comfortable with researchers or clinicians having conversations about fertility, reproduction, or sexuality with their adolescent. Health professionals and parents often agree that fertility is a concern when undergoing treatment for cancer, but there is disagreement whether the adolescent should be informed. Parents may misjudge their child's ability to understand and process this information, and this may prevent them from enrolling or including their child in research studies.^{33–35} To understand the biases in assessing

reproductive concerns for adolescents with cancer, studies need to account for reasons of non-response. Parents may not agree to participate in studies for a variety of reasons, including inconvenience and distrust. However, failure to document these reasons makes it difficult for consumers to determine generalizability. Reasons for non-participation should be addressed in the study design. This could be accomplished by asking those that decline participation to complete a short form using standardized reasons for non-participation, such as those recommended by the American Association of Public Opinion Research.³⁶ Comparisons of non-participants and participants should routinely be included in the results.

Conclusions

The needs of children and adolescents both on and off cancer treatment are unique. Fertility preservation, although sometimes difficult to discuss or comprehend, is an important issue to this pediatric population, as it is for the adult population. Prior research in this area has been informative, but there are several opportunities to advance this knowledge with the ultimate goal of providing all pediatric oncology patients with cancer information about fertility preservation. As children and adolescents transition from active patients to survivors, their fertility concerns may change. This highlights the importance of utilizing accurate reproductive concerns instrumentation before treatment and throughout the treatment process to properly assess the evolving needs of these patients. Systematic testing of multilevel fertility preservation interventions across the cancer continuum is needed to improve health outcomes and quality of care.

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Disclosure Statement

None of the authors have any conflicts of interest to disclose.

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