



Pediatric oncofertility: an update

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Abstract: Fertility preservation (FP) in pediatric patients with cancer is an evolving field. In this review, we give a short update on recent scientific advances in the practice of pediatric oncofertility, particularly related to the research involving gonadal tissue cryopreservation from prepubertal patients, which remains experimental. We then focus on recent advances in the implementation of formal pediatric oncofertility programs and barriers in the delivery of FP in this patient population. Finally, we include some of the more recent outcomes data from established oncofertility programs that treat pediatric patients.

Keywords: Pediatric; fertility; preservation; oncofertility; cancer

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Introduction

Oncofertility is a relatively young field (1) that is meant to address the potential detrimental effects that cancer treatment can have on future fertility. The field of pediatric oncofertility, or fertility preservation (FP) in children with a diagnosis of cancer, brings with it multiple layers of added complexity not present when treating adults (2). Issues of consent, equity and other ethical pitfalls exist.

Childhood cancers vary widely in treatment and outcomes, but overall survival based on contemporary estimates is over 80% (3). This leaves a large number of patients who survive into adulthood and are subject to the long-term morbidities of cancer treatment, with recent estimates putting that number at close to 400,000 in the United States alone (3). One major long-term effect of cancer treatment is infertility, which is due to the relative susceptibility of the gonads to the detrimental effects of these treatments. Based on data from the Childhood Cancer Survivor Study cohort, males are at higher relative risk of infertility than their female counterparts (2.6 *vs.* 1.3, respectively) (4,5), however both show significantly lower rates of fertility than sibling controls (5,6).

Infertility can be a result of a number of different cancer treatments. This includes chemotherapy, particularly with alkylating agents (7,8) and heavy metals (9). Radiation, either directly to the gonads (10,11), or indirectly through damaging the hypothalamic and pituitary secretion of gonadotropins from the brain (12) have also been shown to have dose-dependent effects on fertility in the long term. Management of some cancers also involves surgical removal of reproductive organs, also leading to direct effects on fertility (13).

Due to the risk of infertility, particularly with higher risk patients, preserving sex cells or gonadal tissue for future use in fertility treatments is an accepted practice with guidelines suggesting referral for these services to all post-pubertal patients, both male and female (14). We recently published a review of contemporary advancements in the field of pediatric oncofertility (15). In this article, we will review the scope of the problem and provide a brief update on the science of pediatric FP, but also aim to focus on and provide an update on recent advances in the delivery of oncofertility care to the pediatric population, which is the focus of much of the literature since our last publication.

Pediatric FP: where is the science?

Currently, there are established protocols that have resulted in live births using gonadal tissue or sex cells obtained from post-pubertal patients prior to initiation of gonadotoxic treatment of cancers (16-18). There has also been a case report of a successful pregnancy and live birth in a patient who had primary ovarian failure using retransplanted, cryopreserved, autologous ovarian tissue collected prior to menarche (19). A mature oocyte has also been obtained from xenotransplanted, cryopreserved ovarian tissue obtained from a 6-year-old female prior to her undergoing gonadotoxic chemotherapy (20). With these promising experimental results, there appears to be hope for eventual clinical success of FP in pre-pubertal females in the near future (21).

In the case of pre-pubertal males, however, success continues to be limited. To date, there has not been successful maturation of spermatogonial stem cells from pre-pubertal human tissue beyond the diploid phase using autotransplantation or xenotransplantation (22), although complete maturation has been achieved using xenotransplanted primate testicular tissue (23,24). While promising, xenotransplantation in both male and female human patients is thought to be less acceptable as it can have unknown effects on human cells (25).

In vitro maturation of stem cells from pre-pubertal testicular tissue is a strategy that is also being investigated. While there has been no success in differentiating stem cells into mature sperm, de Michele *et al.* have been able to obtain haploid cells from long-term culture of frozen-thawed pre-pubertal human testis tissue, suggesting that this approach may eventually lead to successful fertility outcomes (26,27).

Given the rapid advances in the field, studies from both the United States and Europe have shown that cryopreservation of pre-pubertal testicular tissue is acceptable to the majority of parents for the possibility of FP in the future (28-30). The most recent guidelines, however, continue to consider the collection of this tissue experimental and thus only recommend the practice in conjunction with an established research protocol (14).

Delivery of FP care

As the science advances, the clinical delivery of FP services must also progress. While there are well thought out guidelines for FP in adult patients (31) there are multiple

additional complexities for pediatric patients that must be considered. Despite this, recommendations for the discussion of FP options with families of patients with a new diagnosis of childhood cancer have existed for over a decade (32). Where these recommendations do exist, implementation seems to be less straightforward. FP is often not discussed in clinical interactions with families, which can lead to disappointment and regret from some patients (33). A survey of providers in Sweden showed that of the responding physicians (all of whom were involved in pediatric oncology care), the potential impact of cancer care on fertility was only discussed with 62% of male patients and 57% of female patients (34), where more recent estimates suggest that rates may be much less than this (35).

Even patients within an established network of centers that offer tissue cryopreservation, 39% of samples were collected from patients that had already initiated gonadotoxic treatment (36), suggesting that there is often a delay in consultation. These findings underscore the importance of having an organized way of identifying, referring and counselling these patients to allow timely care.

In order for this to occur, there should be an organized way for these services to be offered and performed. This can be challenging because it necessitates the involvement and coordination of multiple providers and specialties. Moravek *et al.* describe the formation of a pediatric oncofertility program and its ideal elements (13). These elements include a program director and an administrative coordinator. Along with central administration, there must be coverage by medical and surgical specialties including pediatric oncology and endocrinology, pediatric surgery, pediatric urology and pediatric/adolescent gynecology. While medical and surgical specialties are integral in the initial consultation and subsequent surgical management of FP, having a pathology team that is experienced in FP techniques is essential in a successful program. Proper processing and storage can also involve adult infertility specialists and facilities that coordinate with pediatric providers. While there is even a textbook chapter dedicated to setting up this type of program in the pediatric setting (37), navigating the referral patterns, interdepartmental relationships, insurance concerns and other challenges requires an individualized workflow for each participating center (38).

Other supportive services that can also be extremely valuable in appropriate delivery of pediatric oncofertility care include social work and behavioral/mental health participation. These vital ancillary services can assist with the logistical and financial concerns along with

the psychosocial stress of the potential of infertility that accompanies a diagnosis of childhood cancer (13).

Another element of appropriate delivery of care is the development of evidence-based patient education materials and decision aids (39). These can assist in standardizing the information that is given to patients and parents, which improves understanding of the options and confidence in decision-making (40). Publicly available resources do exist, but not all are specific to the pediatric population (41,42).

With these recommendations, barriers remain in the implementation of successful delivery of pediatric FP. In a systematic review by Anazodo *et al.* (43), the literature regarding models of care (MOC) for pediatric oncofertility was reviewed and themes were identified to suggest major areas of improvement in the delivery of care. Their group identified the following nine domains of oncofertility MOCs (a number of which have already been discussed):

- (I) Communication;
- (II) Oncofertility decision aids;
- (III) Provision of care, including age appropriate care;
- (IV) Referral pathways between cancer and FP services;
- (V) Documentation of oncofertility discussions, decisions and procedures;
- (VI) Training of cancer and fertility healthcare professionals (HCPs) to deliver oncofertility care;
- (VII) Medical supportive care during FP;
- (VIII) Reproductive care in survivorship;
- (IX) Fertility-related psychosocial support.

Within the nine domains of oncofertility MOCs, the major areas of improvement that were identified included the importance of providing high quality information across a variety of different formats (including decision aids) to patients, assuring care is delivered in a prompt manner, assuring age-appropriate consultation and recommendations, better defining the roles of practitioners within the care model, and assuring adequate communication and coordination between the various professionals involved in pediatric oncofertility care.

Although these areas do not address all of the barriers to delivering pediatric oncofertility care, they do highlight a number of areas where the literature has not provided consistent solutions and recommendations in the form of guidelines.

Contemporary outcomes

There is abundant literature on establishing and implementing a pediatric oncofertility program, but

there remains a lack of information on the effects that a formal pediatric oncofertility program can have on patient satisfaction and utilization of FP. In fact, no pediatric-specific literature has been published to date. At this point, information that is “pediatric-specific” must be extrapolated from programs that include both adolescents and young adults (AYA). With regard to patient satisfaction, Kelvin *et al.* showed an increase in satisfaction with the resources and amount of information provided that was significant regardless of gender or diagnosis after establishment of their oncofertility program (44). In the same study, 96% of males and 99% of females who received and read informational materials in the program considered them to be helpful.

The effect of establishing a dedicated AYA oncofertility program has similarly been shown to affect utilization of FP services. In a study from Canada, Lewin *et al.* reported that after establishment of their oncofertility program geared toward AYA, both documentation of infertility risk discussion and utilization of FP increased from approximately 55% to 85% (45). Lopategui *et al.* from the United States described outcomes of their formal oncofertility program that did include a minority of pediatric patients (46). During the first year of their program, the percentage of oncology patients undergoing FP increased over 6-fold to 19.3% compared to 3.3% in the 5 years prior to the establishment of the program. There is a large disparity in the numbers reported by these different institutions (likely reflecting differences in coverage of these services in different countries), but they both show a substantial increase in utilization after establishment of a formal oncofertility program. This underscores the importance of these programs in increasing access to these services in the pediatric population.

Another area that has been investigated with regard to pediatric oncofertility are the awareness, perceptions and attitudes of adult survivors of childhood cancer toward potential infertility (47). In a study from the St. Jude survivorship cohort, Lehman *et al.* reported that while most childhood cancer survivors (61.9%) perceived themselves at increased risk for infertility, laboratory-evaluated impaired gonadal function was found in 24.3% of female and 55.6% of male survivors. Concordance with laboratory-demonstrated subfertility was low (Cohen’s $\kappa < 0.19$) with 19.7% of male and 43.6% of female survivors overestimating their risk and a significant number of male (16.3%) and female (5.3%) survivors who underestimated their risk of infertility (48).

Using a different cohort from Nationwide Children’s

Hospital (49), Lehman demonstrated again that the majority of patients in that cohort were aware of an increased risk of infertility (82.4%) from childhood cancer treatments, but 48.9% had never been tested and did not know their fertility status. Ten percent of patients in that study claimed that infertility had negatively impacted their relationships, which was mainly found in partnered survivors who had no children or desired additional children. While this is the case, there is evidence that those individuals who undergo proper referrals and opt for oncofertility care are typically those that would benefit from it the most. A study from the Oncofertility Consortium's National Physicians Cooperative evaluating 114 female patients who underwent ovarian tissue cryopreservation showed that those opting for this treatment were predominantly patients with leukemias, myeloproliferative and myelodysplastic diseases, malignant bone tumors and soft tissue sarcomas (50). This group of patients had the highest overall risk of infertility in the cohort and were, thus, the most likely to benefit from FP techniques.

These studies not only underscore the importance of early FP discussion and treatments in the pediatric period, but also highlight the need for accurate, personalized prognostic information to aid in decision making. They also show the importance of long-term follow-up and discussion with survivors, as the information that is initially shared with parents is often not carried with the patient into adulthood. Because of this, the authors recommend that fertility testing and treatment should be routinely offered as patient circumstances and interest in fertility can change and evolve over time (49). These further encounters may best be had by adult reproductive endocrinology and andrology specialists, which can be a part of the pediatric oncofertility team (13). FP offered in the pediatric period would potentially keep options open as these patients reach an age when fertility becomes a concern.

Conclusions

Pediatric oncofertility remains a developing field with significant challenges and imperfect solutions. Current literature emphasizes a focus on improving the delivery of this care to appropriate pediatric cancer patients and advancing the science to extend fertility options to pre-pubertal patients. While further research is needed in both of these areas, survivorship studies show that these continued efforts can have a positive impact on an ever-increasing number of patients.

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