Review Article

Current standing and future directions in pediatric oncofertility: a narrative review

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Abstract: In this narrative review, we discuss the epidemiology and pathophysiology of infertility in childhood and adolescent cancer. We also review the current guidelines and ethical issues related to pediatric oncofertility. Finally, we present recent advances in basic science and translational research in pediatric fertility preservation (FP).

Keywords: Childhood; pediatric; fertility; adolescent; preservation; oncofertility

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Introduction and definition

Cancer in children and adolescents is relatively uncommon, but is estimated to affect over 15,000 patients a year in the United States (1) with the most common types being leukemias and lymphomas, central nervous system tumors, soft tissue sarcomas, neuroblastomas and kidney tumors. Survival rates have improved dramatically in the last few decades with an overall 5-year survival of 83.5% (2). With many of these patients surviving into adulthood, the long-term effects of treatment are becoming better understood, one of which is infertility. The American Society of Clinical Oncology (ASCO) first published guidelines recommending that referral for fertility preservation (FP) be offered to patients of reproductive age in 2006 (3). With intensified interest in FP in cancer patients, the term oncofertility was coined and has since become its own area of clinical practice and research (4). Numerous guidelines and recommendations have been published, including some that address pediatric patients, but few advances in clinical practice have been realized in the last decade. While awareness of the issue has increased, practice patterns regarding discussion of FP with appropriate patients varies widely even among oncologic specialists (5). In this narrative review, we will discuss the epidemiology and pathophysiology of infertility in childhood and adolescent cancer, review current guidelines and ethical issues in pediatric oncofertility, and present recent advances in basic science and translational research in pediatric FP.

Scope of the problem and pathophysiology

With the current population of childhood cancer survivors estimated at 380,000 in the United States (2) and incidence of pediatric cancers increasing slightly in recent years (1), the number of these patients reaching childbearing age is significant and is likely to continue to increase. The incidence of infertility in patients receiving chemo- and radiation therapy varies widely with age and gender, but remains significant. In male patients, rapidly dividing, differentiating spermatogonia are very sensitive to damage by radiation and cytotoxic chemotherapy, which leaves later stage germ cells that continue to differentiate without being replaced by new cells derived from spermatogonia. This results in a depletion of the remaining later-stage differentiating cells and eventual oligo- or azoospermia (6). In females, chemo- or radiation therapy can cause apoptosis of primordial follicles. This causes a reduction

of anti-Müllerian hormone (AMH) levels and leads to the recruitment of surviving primordial follicles. This, in turn, causes depletion of the ovarian reserve or "burnout" (7) and premature ovarian failure. Younger patients seem to be at lower risk than older patients (8) and female patients are at a lower risk than males due to the effects of chemotherapy on the testis compared to the ovary (9). The type of cancer therapy also has a large impact on infertility risk. ASCO categorizes the likelihood of infertility based on various chemotherapeutic regimens into low (<20%), intermediate (20–80%) and high (>80%) risk of infertility (3). Commonly used alkylating agents such as cyclophosphamide subject a patient to the highest risk, and it has been suggested that a "summed alkylating agent dose score" be used to predict risk for gonadal injury and subsequent infertility (10). Radiation therapy also has a significant effect on fertility with cumulative doses over 4 Gy to the testes (11), 30 Gy to the hypothalamus-pituitary axis, and >5 Gy to the uterus and/or ovaries (10). Because infertility due to cancer treatment is multifactorial, overall rates of infertility are difficult to ascertain. It is estimated, however, that the risk of infertility is 2.5 times higher in male cancer survivors than their healthy siblings and approaches 50% (11).

Why address this issue?

While fertility may not be the most pressing issue in the management of pediatric patients with newly-diagnosed cancer, it has been demonstrated that as survivors aged, they and their families had significantly more interest in fertility (12). In fact, over 75% of childhood cancer survivors expressed a desire to have children in the future (13,14). Parents and adult male survivors of childhood cancer were also shown to have a significant amount of regret when FP was not pursued at the time of initiation of therapy (12).

Current recommendations

In general, guidelines recommend that patients be counseled on the possibility of infertility regardless of age and that appropriate patients be referred for discussion of FP. Guidelines for pediatric patients can be divided according to gender and pubertal status. One, example of consensus guidelines following this pattern are the ASCO pediatric consensus guidelines for newly diagnosed pediatric oncology patients regarding oncofertility.

ASCO has the following guidelines for male children and adolescents with a new cancer diagnosis (15):

(I) For post-pubertal patients, a semen sample can be obtained through masturbation or testicular sperm aspiration and cryopreserved.
  (i) It is generally recommended that, due to the risk of genetic damage from chemotherapy, the sample be collected before the initiation of therapy.
  (ii) Cryopreservation of sperm has been studied extensively and specimens have been used, resulting in successful pregnancy.

(II) Hormonal suppression to preserve gonadal tissue has not been proven to be successful and is not recommended.

(III) Testicular tissue cryopreservation from pre-pubertal patients is noted to be experimental at this time and it is recommended that this only be offered in conjunction with established research protocols.

In the case of female patients, the ovary is more resistant to deleterious effects of chemotherapy, but both radiation therapy and chemotherapy have been shown to increase risk of premature ovarian failure (16) and have a negative impact on pregnancy rates (8).

Current guidelines from ASCO suggest the following regarding female patients (15):

(I) Post-pubertal patients can be offered cryopreservation of oocytes, as this is no longer considered experimental and is now consistent with established guidelines (17).

(II) Post-pubertal females who have a partner can also be offered embryonic cryopreservation. Either of these options should, however, be performed at centers with sufficient expertise.

(III) Delays in the initiation of therapy should be minimized, as oocyte collection requires prior ovarian stimulation.

(IV) In female patients undergoing pelvic radiation, surgical relocation of the ovaries (oophoropexy) has been described, but is not always successful due to radiation scatter and possible remigration.

(V) Ovarian tissue cryopreservation and transplantation, particularly in pre-pubertal patients, does not require ovarian stimulation but remains experimental and should only be offered in conjunction with an established research protocol.

In the pediatric setting, it is recommended that both parent and patient be involved in the decision making process and that both consent and assent be obtained. In both male and female patients who are pre-pubertal, there are no

current options other than gonadal tissue cryopreservation, although methods for using this tissue in future fertility options remain investigational and unproven (15).

Barriers and ethical issues

In spite of established guidelines, FP is often not discussed with pediatric patients (18). Surveys of pediatric oncologists regarding their practice patterns showed that younger age and female gender were seen as barriers to discussion of FP techniques (19,20).

A recent systematic review evaluated and categorized various barriers to FP discussion among a variety of healthcare providers (21). Overall, providers were found to have a high level of awareness of treatment effects of fertility, but significant gaps existed in knowledge about FP options that kept some providers from initiating discussions on the topic. These knowledge gaps included the cost and details of FP procedures, facilities and specialists for FP referrals, how to approach a conversation about FP, and options available for young female patients. Provider sense of comfort was found to be a barrier to discussing FP, particularly with regard to discussion of sexual practices and activity privately or with parents. The prospect of bringing up topics that are not appropriate for the age or sexual maturity of the patient and discussing the use of erotic materials in sperm banking were also found to be a barrier to discussion. Patient and parental factors were also reported to be barriers to FP discussion. Patient factors brought up in the analysis include poor prognosis, positive HIV status and inability of patients to afford the treatment. The prospect of bringing a new issue to the table with an already stressful diagnosis was also a recognized barrier to FP discussion as were issues of consent and undue parental influence in a very personal decision for the patient. Finally, seven of the studies included in the review also brought up a lack of educational material as a barrier to addressing FP.

While guidelines do exist and FP discussions are recommended with adult patients, ethical issues remain with children and adolescents, particularly those in the pre-pubertal period. These issues can be divided into ethical concerns at the time of FP treatment and ethical concerns in the future. Ethical concerns at the time of FP treatment include possible delay in timely cancer treatment for the possible future benefit of fertility (22) and a possible lack of comprehension of the family regarding potential for fertility. Ethical consideration must be given to the potential distress and discomfort to the child from the FP treatment, along with surgical and anesthetic risks of the treatments themselves possibly outweighing the benefits of the treatment (23). This is particularly true in cases where the FP treatment is experimental or where the possibility of successful treatment is low.

Possible ethical concerns in the future include the impact of FP treatment on future gonadal function, the high cost of treatment and storage of gonadal tissue making it unavailable to patients without financial means (24) and the fate of the tissue if the patient does not survive (22). Future ethical issues would also include the possibility of re-introduction of malignant cells with transplantation of gonadal tissue (25) and possible compromised health of the offspring arising from FP treatments (26,27). These actual and potential issues underscore the need for an individualized approach to assessing risks and benefits of FP treatment, particularly in the pediatric population.

As alluded to, one of the major barriers to FP is the monetary cost of related procedures and long-term cryopreservation of sperm, oocytes or gonadal tissue. For example, in the case of oocyte or ovarian tissue preservation, the initial cycle or surgery for retrieval costs approximately $10,000 and storage costs an additional $300–$500 per year (28). Sperm retrieval is less costly, especially if a sample can be obtained by masturbation, but storage costs are similarly expensive (29). Recent improvements to insurance coverage for FP and advocacy organizations that assist patients financially (15) are some ways that this barrier can be overcome, but access is still in not universal in this population.

Recent publications demonstrate that establishing a formalized oncofertility program results in improved documentation of FP discussions (30) and may increase the likelihood of appropriate referrals to FP specialists (31). While these studies are not specifically related to pediatric patients and providers, there is likely benefit from having organized programs and referral patterns in overcoming barriers and providing appropriate care and counseling.

Experimental therapies using immature gonadal tissue

As discussed earlier, pre-pubertal patients diagnosed with cancer currently have no proven option of FP. Gonadal tissue can be collected on these patients, but guidelines suggest that this only be offered in conjunction with an established research protocol. While this is the case, there are centers that offer tissue preservation in hopes of future

scientific progress. The main problem in this population in developing mature sex cells (sperm and oocytes) from stem cells in immature gonads.

In the case of female patients, ovarian tissue cryopreservation (OTC) and retransplantation has been shown to be a promising option and progress has come to the point where some recommendations exist to offer this to carefully selected pre-pubertal patients (32). In this approach, cryopreserved tissue is thawed and grafted into orthotopic sites (residual ovary, broad ligament or nearby pelvic tissue) (33). Advantages of this approach include the ability to retrieve the tissue regardless of pubertal status, and it circumvents delaying the initiation of the girl's oncologic therapy. One major disadvantage is the potential re-introduction of malignant cells in malignancies that may affect the ovaries, although this has not been reported to date (34).

OTC with retransplantation has resulted in successful pregnancy and live birth in 86 cases with tissue collected from post-pubertal patients (35). There has been only one reported case of successful spontaneous pregnancy from retransplanted ovarian tissue collected prior to menarche for subsequent primary ovarian failure (36). While this is an isolated case, it does hold promise for future FP options in pre-pubertal female patients.

Another promising approach for female FP is xenotransplantation of cryopreserved ovarian tissue. This approach has been successfully tested by grafting pre-pubertal ovarian tissue from a 6-year-old female patient with Wilm's tumor into immunocompromised mice (37). The group was able to retrieve a completely mature oocyte from the xenograft without any exogenous hormone administration. After complete excision, the graft was found to have follicles in all developing stages, suggesting that the tissue was synchronized with the HPA axis of the mouse.

In vitro maturation (IVM) of primordial follicles has also been attempted on cryopreserved ovarian tissue (38), and while maturation rates were much lower for pre-pubertal tissue, maturation was successful in some cases. While no usable oocytes could be retrieved in tissue from patients younger than 5, this option also holds promise for FP in some pre-pubertal female patients.

In male patients, sperm cryopreservation is a routinely performed option for FP and has provided results including pregnancy and healthy offspring. This method has been used since the first successful pregnancy was achieved with frozen/thawed sperm in 1953 (39). Prepubertal males, however, do not produce mature sperm. Attempts at producing mature sperm from spermatogonial stem cells (SSCs) in pre-pubertal testicular tissue is still in early experimental stages compared to tissue cryopreservation and oocyte maturation in pre-pubertal females. Animal models show promise in transplantation of SSCs into the seminiferous lumen of germ-cell depleted hosts (40). Results, including healthy offspring in mice and production of mature sperm in non-human primates, have been achieved (41,42), but the propagation required for successful transplantation in humans has proved difficult due to only short-term survival of SSCs *in vitro* (43).

Another approach is grafting of cryopreserved immature testicular tissue. While this approach has successfully resulted in sperm and healthy offspring in animal models (44-46), transplantation of human immature testicular tissue have not resulted in maturation beyond the stage of spermatocyte (47).

A third possible approach for using cryopreserved pre-pubertal testicular tissue is spermatogenesis *in vitro* from SSCs. This has been successfully tested in the mouse model with resultant sperm having been successfully used in ICSI (48,49). Attempts on pre-pubertal human testicular tissue have successfully resulted in somatic cells maturing to a post-pubertal phenotype, but were unsuccessful in producing mature sperm (50). This is likely due to the fact that major differences have been found in the response of spermatogonia to gonadotropins between mice and primates (51).

In spite of the current techniques involving cryopreservation of gonadal tissue being considered experimental, a recent survey of members of the Oncofertility Consortium Global Partners Network demonstrated that at least 16 centers worldwide offer testicular tissue cryopreservation and 26 centers offer ovarian tissue cryopreservation to pre-pubertal patients (52). Given the success with OTC in the investigational setting, this would seem appropriate; however, significant hurdles remain in using cryopreserved testicular tissue to produce mature sperm.

Conclusions

Oncofertility remains an emerging field, particularly in the pediatric setting. Fertility and FP become increasingly important to patients as they enter adulthood and should thus be discussed with children and adolescents that are to undergo gonadotoxic treatments for a new diagnosis of cancer. Barriers remain in facilitating appropriate discussion of this topic and formalized oncofertility programs may help in providing access and realistic information to patients

and parents. Established options for FP exist for both male and female post-pubertal patients and although promising advances have been made for pre-pubertal patients, FP techniques remain experimental in that population.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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