Published in final edited form as:

J Adolesc Health. 2019 May ; 64(5): 563–573. doi:10.1016/j.jadohealth.2018.10.297.

Development of a Pediatric Fertility Preservation Program: A Report from the Pediatric Initiative Network of the Oncofertility Consortium

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Abstract

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Implications and Contribution: Evidence from this literature review provides guidance from the Pediatric Initiative Network of the Oncofertility Consortium for health care providers establishing a pediatric fertility preservation program.

Disclosures:
Dr. Pavone serves on the Ferring advisory board. All other authors have no conflicts of interest.

Infertility is known to decrease quality of life among adults. In some cases, infertility is caused by medical conditions and/or treatments prescribed in childhood, and using methods to protect or preserve fertility may expand future reproductive possibilities. Structured programs to offer counseling about infertility risk and fertility preservation options are essential in the care of pediatric patients facing fertility-threatening conditions or treatments, yet multiple barriers to program development exist. This report was developed from the institutional experiences of members of the Pediatric Initiative Network of the Oncofertility Consortium, with the intent of providing guidance for health care providers aiming to establish programs at institutions lacking pediatric fertility preservation services. The mechanics of building a fertility preservation program are discussed, including essential team members, target populations, fertility preservation options (both established and experimental), survivorship issues, research opportunities, and ethical considerations. Common barriers to program development and utilization, including low referral rates and financial concerns, are also discussed, and recommendations made for overcoming such barriers.

Keywords

Fertility Preservation; Child; Adolescent; Program Development; Tissue Preservation

Infertility is a potential consequence of several childhood and adolescent medical conditions and/or their treatments, and may be mitigated by an expanding range of fertility preservation (FP) options. The American Society for Clinical Oncology (ASCO), American Society for Reproductive Medicine (ASRM), and American Academy of Pediatrics (AAP) have all put forth guidelines recommending that providers discuss fertility preservation with patients prior to gonadotoxic therapy,[1–3] but referral rates are still low.[4–7] Establishing a structured FP program has been shown to increase both patient satisfaction[8] and FP utilization rates.[9,10] The Oncofertility Consortium was established in 2007 to create an interdisciplinary global network committed to furthering FP research and clinical care, and currently has over 180 member clinics/centers. Subsequently, the Pediatric Initiative Network (PIN) of the Oncofertility Consortium was established, dedicated to improving fertility-related care specifically for children and adolescents at risk for future fertility impairment. Members of the PIN include health care providers and researchers in the fields of reproductive endocrinology (REI), pediatric and adolescent gynecology (PAG), and pediatric oncology, urology, endocrinology, and mental health from over 30 institutions around the world. The PIN meets regularly via phone conference to discuss program development and barriers to care, best practices, and research opportunities. Unfortunately, PIN members have faced many barriers in trying to develop fertility counseling and preservation programs at their home institutions, and there is very little in the literature to provide guidance. The objective of this manuscript is to combine the experiences of PIN members with a narrative review of the literature to provide guidance for health care providers aiming to establish institutional programs where pediatric FP services are needed.

METHODS

A literature search was conducted of the PubMed and MEDLINE databases using combinations of the following search terms: fertility preservation, program development, barriers, referral, adolescents, pediatrics, childhood, cancer, oncofertility, gonadotoxicity, ovarian failure, ovarian insufficiency, premature menopause, infertility, testicular failure, transgender, chemotherapy, radiation, gonads, oocyte cryopreservation, ovarian tissue cryopreservation, sperm cryopreservation, testicular tissue cryopreservation, distress, decision making, decision aids, survivorship, hormone replacement therapy, puberty induction, reproductive health, contraception, sexual function, ethics, minors. There were no restrictions placed on year of publication. The Oncofertility Consortium and Childrens Oncology Group website were also searched for practice recommendations. Only English-language and human studies were included, except where describing animal studies of experimental fertility preservation techniques. All authors agreed on both the search terms and included articles. Where there were gaps in the literature, authors were asked to contribute their institutional experience and expertise as PIN members, particularly with regard to experiences and challenges surrounding program development.

FIRST STEPS

The authors agree that an essential first step in developing a pediatric fertility preservation program is to identify a director who will advocate for the program and organize the members of the team. A physician typically fills this position, although some institutions have nurses or basic scientists fulfilling the role. Prior to formalizing a program, the program director should attempt to secure institutional support for additional personnel and space requirements. A suggested list for an institutional “ask” is outlined in Table 1. There are several medical societies that have published guidelines recommending fertility preservation counseling in patients facing gonadotoxic therapies that can be presented to institutional officials, including those from the National Comprehensive Cancer Network, ASCO, AAP, ASRM, Endocrine Society, and World Professional Association for Transgender Health.[1–3,11–13] The US News and World Report rankings of children’s hospitals now awards points for hospitals with fertility preservation programs. A needs assessment should be performed by defining the target population and estimates of anticipated volume, both institutionally and regionally, and a business plan should be developed to justify the necessary resources for the program. A list of current centers with formalized fertility preservation programs can be found on the Oncofertility Consortium website (http://oncofertility.northwestern.edu/find-a-clinic-or-center); this information can be helpful both for demonstrating to institutional officials that fertility preservation programs are becoming standard at many institutions, as well as for highlighting the need for fertility preservation care within the institution’s catchment area.

ASSEMBLING THE TEAM

A successful pediatric FP program requires collaboration across multiple medical and surgical specialties, with suggested team members listed in Table 2. A systematic multidisciplinary approach to fertility risk assessment and preservation consultation

increases programmatic success and referral rates.[14,15] Therefore, it is helpful to identify champions from each specialty division to lead fertility initiatives and assume responsibility for consult-related communication.[16] The role of division champion may be filled by various clinical staff (nursing, nurse practitioners, physician assistants, and/or physicians), depending on local resources and established clinical practices.

Pediatric FP techniques rely on timely referrals and an efficient workflow to minimize treatment delay. For care coordination, the importance of a Patient Navigator cannot be overstated. The Patient Navigator shepherds patients through a complex medical system, providing a single point of contact for referring practitioners, patients and the multidisciplinary team. Many PIN programs have filled this position with a nurse or nurse practitioner, but the roles and responsibilities can be fulfilled by a variety of educational backgrounds (Table 1). Key roles include ensuring timely consult completion, ongoing patient engagement, and coordination of FP procedures.[17] In programs without a patient navigator, a single point of contact should still be identified, for example the program director, to facilitate communication across disciplines.

Crucial steps in the FP consultation are 1) infertility risk assessment; 2) discussion about FP options; 3) referral to fertility specialists; and 4) coordination of FP procedures. Risk assessment and FP counseling may be provided by Pediatric Endocrinology, Oncology, PAG, Adolescent Medicine, REI, Pediatric Urology, Andrology, mental health providers, and/or the Patient Navigator, depending on the institution. It is imperative that referring services provide information about planned therapy and timeline to inform risk assessment and FP options. FP interventions may be performed by PAG, urology, surgery, and/or REI. Additional team members may include pathologists, research coordinators, social workers,, quality improvement specialists, bioethics experts, and business directors.

One possible workflow begins with the patient navigator receiving all consultation information (diagnosis, treatment information, and timeline) in a centralized pool with several points of entry (pager, phone, email, medical record). Staff education and decision aids may be utilized to assist with consultation standardization and flow. Risk assessment and available FP options are explained during the initial consultation. The patient navigator then performs timely follow-up to answer questions and coordinates any requested FP procedures. It is essential that workflows are also developed for weekends and holidays, since time is often a critical element.

IDENTIFYING TARGET POPULATIONS

Once the core team is established, it is important to identify populations at risk for infertility.

Childhood and Adolescent Cancer

The majority of pediatric FP studies have been conducted in oncology. Compared to siblings without a cancer history, female survivors have a relative risk of pregnancy of 0.81 (95% CI 0.73–0.90) and male survivors a hazard ratio of 0.56 (95% CI −0.49 to 0.63) for fathering a pregnancy.[18,19] Similarly, the relative risk of infertility in male survivors compared to siblings is 2.64 (95% CI 1.88–3.7),[20] and 1.34 (95% CI 1.12–1.60) in female survivors.[21]

Accordingly, newly diagnosed cancer patients should be counseled about their risk of infertility based on planned treatment.[1,22,23] Infertility can result from removal of reproductive organs or destruction of reproductive germ cells.[24,25] Males may experience temporary azoospermia (absence of sperm) following treatment that resolves as germ cells re-initiate the maturation process, or permanent azoospermia as the result of more extensive germ cell destruction.[24] For females, exposure to gonadotoxic therapies can result in ovarian insufficiency during or shortly after treatment.[26] Others, with less extensive damage to their immature oocytes, may retain reproductive capacity following treatment, but enter menopause prematurely, thereby shortening their reproductive window.[27–30]

Broadly, it has been well documented that alkylating agents (e.g., procarbazine, cyclophosphamide, busulfan) are toxic to testes and ovaries in a dose-dependent fashion.[31,32] Heavy metals (e.g. cisplatin) also impact fertility.[33] The cyclophosphamide equivalent dose (CED) scoring system, available as an online calculator, can be used to compare gonadotoxicity of different alkylating agents.[32,34] Radiation involving the gonads also diminishes fertility in males and females in a dose-dependent manner.[35,36] Radiation to the brain can impair the hypothalamic-pituitary-gonadal axis in both sexes causing gonadotropin deficiency, managed with hormonal interventions.[37]

Non-Oncologic Populations at Risk

Emerging information highlights other at-risk pediatric populations that could benefit from FP. Youth with systemic lupus erythematosus, vasculitis, and some forms of renal disease may be exposed to moderate-high cyclophosphamide doses; however, FP is offered to a minority of these patients.[38–40] Additionally, youth undergoing stem cell transplantation (SCT) for non-malignant conditions, such as hematologic conditions, should be counseled about infertility risk and FP.[41] Adolescents with gender dysphoria may be exposed to gender affirming treatments that may affect fertility, such as testosterone or estrogen.[13]

Reproductive capacity may also be affected by gastrointestinal/genitourinary surgery, and is impaired in several congenital and acquired conditions like cystic fibrosis, hemochromatosis, galactosemia, autoimmune ovarian insufficiency, spina bifida, fragile X syndrome, Down syndrome, Turner and Klinefelter syndrome, and other differences of sex development (DSD).[42] While little has been done to explore fertility-related interventions in most of these conditions, studies have shown 1) FP may be effective for females with Turner syndrome (particularly those with mosaicism)[43]; 2) micro-dissection testicular sperm extraction is successful in ~50% of males with Klinefelter syndrome, and optimally performed at 15–30 years of age[44–46]; and 3) some youth with DSD have potentially viable gonadal germ cells.[47] As in some oncologic populations, FP discussions may need to include other considerations such as 1) potential pregnancy-related complications to the mother and/or fetus; 2) possibility of passing on a genetic mutation/heritable disease; 3) options for gonadal tissue use if a pregnancy is not possible or desirable; 4) ethical dilemmas in patients with some degree of cognitive impairment. It is also important to note key differences between each at-risk group. Some clinical scenarios may allow more time for contemplating fertility interventions (e.g. Klinefelter syndrome) than occurs in the setting of a new cancer diagnosis; on the other hand, FP will not be a viable option for every at-risk group (e.g.

testicular regression syndrome). Thus counseling should be individualized and may need to focus on alternate options for parenthood; a recently published Clinical Report from the American Academy of Pediatrics outlines these considerations along with specific talking points at various ages/developmental stages.[42]

FERTILITY PRESERVATION OPTIONS

A comprehensive pediatric fertility preservation program should offer counseling to males and females of all ages and pubertal stages.

FP Options for Females

Established FP options for females include ovarian transposition, shielding from radiation, and oocyte/embryo cryopreservation (freezing). Ovarian tissue cryopreservation (OTC) is currently considered experimental in the United States, but is performed as an established FP procedure in parts of Europe and Israel; it is the only FP option for prepubertal females, and is increasingly being offered both abroad and in the United States.[48] Gonadotropin releasing hormone analogues for ovarian suppression are commonly used, but the effectiveness data are mixed and this option is also still considered experimental.

Mature Oocyte Cryopreservation—Mature oocyte cryopreservation involves ovarian stimulation with gonadotropins for 8–14 days and surgical retrieval of oocytes under transvaginal ultrasound guidance with conscious sedation. In postmenarchal females (those who have begun to menstruate), this method is the most likely to result in subsequent pregnancy, and should be offered if ovarian stimulation and oocyte retrieval may safely be performed.[22] Outcomes from mature oocytes cryopreserved in post-pubertal but pre-menarchal patients remain to be determined, as these patients have not yet attempted conception.[49,50] Stimulation can be initiated regardless of menstrual cycle phase (“random start protocol”), resulting in minimal treatment delays.[51,52] Facilities must confirm there is no lower age or upper body mass index limit to performing these procedures and that those administering anesthesia are comfortable sedating adolescents. Additionally, because many adolescents are not sexually active, providers may consider referral to a specialized mental health professional, both alone and with a parent/guardian, to review the process and confirm assent to this rather invasive procedure.[53]

Since data on pregnancy and live births following oocyte cryopreservation in cancer patients are limited, patient counseling is based on success rates extrapolated from other populations, including young oocyte donors.[22] As cryopreservation via vitrification and thawing techniques have evolved, mature oocyte cryopreservation has been associated with steadily improving pregnancy rates of up to 38–55%, similar to that with fresh oocytes.[54–57] For optimal results, oocyte retrieval should occur prior to starting cancer therapy.[58] It is important to establish a relationship with an REI who can schedule patients urgently and is sensitive to the needs of adolescents and their families.

Ovarian Tissue Cryopreservation—OTC involves surgically removing and cryopreserving ovarian cortical tissue for potential future fertility and hormone restoration.[59] The requisites for Institutional Review Board (IRB) approval are institution-specific. OTC

has been carried out in children of all ages, and has been shown to be safe and effective, with less than 1% risk of minor complications, same-day discharge for most patients, and no treatment delay.[60–69] Over the last 17 years, OTC has become a more accepted FP method for pediatric and adolescent cancer patients globally,[70] with a growing number of centers publishing their experience.[14,61,65,67,68,71–74]

The recommended technique is laparoscopic unilateral oophorectomy (partial or total), ideally performed in combination with other necessary procedures, e.g. port placement, under one anesthetic exposure.[69] Special care is taken to avoid unnecessary handling of the ovarian cortical region, where the highest density of primordial follicles, or reserve of potential oocytes, are present.[75] The mesovarium is divided medially to laterally, and the ovarian artery divided last.[76] Technique is particularly important in prepubertal girls who have an average ovarian volume is approximately 1 ml, but the largest primordial follicle pool.[35,77] Once removed, the ovary is placed in media, transported to the pathology or embryology laboratory, divided into cortical strips, then cryopreserved via slow freezing or vitrification. A portion of the cortical tissue may be submitted separately for routine histology and/or for research purposes. The tissue storage site, both for patient use and research tissue, should be determined in advance. An ideal center would have extensive experience with storage of cryopreserved reproductive tissues and offer a discounted storage fee to fertility preservation patients.

Optimal use of cryopreserved tissue for fertility or hormone replacement is under active investigation. Ovarian cortical strips contain mostly quiescent primordial follicles, but studies suggest these follicles can survive and grow to antral stage *in situ*,[78] and secondary follicles encapsulated in alginate hydrogel can be grown and matured *in vitro*.[79] While *in vitro* follicle maturation could provide future fertility, unlike re-transplantation, this method does not restore endocrine function. Over 130 births have been reported following OTC, including one peripubertal and one prepubertal patient at the time of oophorectomy.[80–85] A recent meta-analysis suggests the live birth rate and restoration of hormonal function are greater than 35% and 65%, respectively.[86] Unfortunately, OTC samples from patients with leukemia, breast, gastric, uterine, and cervical cancers have been shown to contain metastatic disease,[87–89] introducing the risk of reseeding cancer after transplantation. As a result, new innovations in restoring ovarian function in a safe and consistent way are being investigated.[89,90]

FP Options for Males

Male FP options include gonadal shielding from radiation, sperm cryopreservation, and testicular tissue cryopreservation (TTC). In male children and adolescents with cancer, the risk of infertility is greater than their female counterparts due to the relative chemo- and radiosensitivity of testicular germ cells.

Sperm Cryopreservation—Sperm cryopreservation is the most established option for male FP, and should be offered to all peri- and postpubertal adolescents with a fertility-threatening condition. Semen quality and DNA integrity may be compromised after a single course of chemotherapy. Stage of pubertal development is considered the best indicator of

spermarche (initiation of sperm production), with sperm cryopreservation typically offered to adolescents who are at least Tanner stage II-III for genital development, with motile spermatozoa reported with testicular volumes as low as 6ml.[91–93]

Semen specimens are most often obtained through masturbation, although penile vibratory stimulation or electroejaculation may also be used.[23,93–97] Testicular sperm extraction (TESE) or microsurgical TESE can also be performed by urology to retrieve sperm from pubertal males before treatment, and are emerging options for post-treatment adults or those with genetic conditions causing oligospermia (low sperm counts).

Testicular Tissue Cryopreservation—A lack of mature sperm limits FP options in prepubertal boys. TTC, an experimental intervention, currently has the greatest potential for this population, although no sperm recovery has been reported from this method to date. TTC involves surgical removal of immature testicular tissue prior to treatment, and cryopreservation via slow freezing. Eligibility for TTC generally includes prepubertal children with high risk of infertility, or patients who are unable to provide an adequate semen specimen. An excisional biopsy through a trans-scrotal approach is ideally coordinated with another surgical procedure (e.g., biopsy, port placement) to minimize anesthetic risk and expedite initiation of treatment.[98] TTC should be discussed with families in the context of an IRB-approved study. TTC has been performed in boys <1–16 years old, [99] with low rates of post-operative complications.[98–100]

TTC is contingent on the future development of techniques for the maturation of spermatogonial stem cells (SSC) into sperm. A variety of SSC-based therapies have been previously described, including the transplantation of SSC into the testis; *de novo* testicular morphogenesis with the introduction of SSC and supporting testicular cells into a decellularized testicular scaffold; autologous grafting and xenografting of testicular tissue; and maturation of testicular tissue in culture. Although these experimental therapies have been promising in animal models, they have yet to be performed in humans.[101]

PATIENT SUPPORT

High rates of fertility-related distress in pediatric cancer patients and their families have been reported[102–105]; however, fertility remains an inadequately addressed aspect of care.[106] While much of this distress can be alleviated with direct attention to treatment-associated fertility risks and FP options by treating practitioners, dedicated mental health professionals can help families work through psychosocial stress related to fertility concerns.[102,103,106]

Even with proper clinical and psychological support, it is often difficult for patients to make FP decisions in the limited time necessary for many cancer treatments. A number of factors influence decision making for FP, both external (delivery and timing of information, referral access) and internal (fear of perceived risks, inability to consider future parenthood); thus, evidence-based patient education materials provided prior to consultation may assist patients in making timely FP decisions.[107] Decision aids have been shown to improve knowledge and decrease uncertainty of choice.[108] Videos providing a brief topic introduction can be viewed before the consult. Patient education tools assist providers in standardizing patient

information. Multiple tools specific to FP are publically available,[109,110] but there are limited data on their use in pediatrics.

SURVIVORSHIP

While discussions about FP are crucial prior to the initiation of gonadotoxic therapy, ongoing reproductive counseling in survivorship is imperative but often overlooked. Managing patients' fertility after therapy is important from both a medical and psychosocial standpoint, since many individuals were very young at the time of diagnosis and have poor recall of fertility conversations. This is also an opportunity to give information about fertility risk and preservation to patients who were too young to be involved in conversations at diagnosis as well as information about fertility treatments, sexual health, contraceptive advice, and HPV vaccination.

Treatment of Gonadal Failure

Hormone production and oocyte reserve are intertwined in females and equally disrupted by cancer therapy, whereas in males the two processes are more distinct, with testosterone production often spared even in azoospermic patients. Screening for gonadal dysfunction in cancer survivors with FSH/LH and either estradiol or testosterone should begin at age 13 in females and 14 in males (if no signs of natural puberty), according to Children's Oncology Group guidelines.[111] The guidelines do not recommend routine semen analysis in males or anti-Mullerian hormone (AMH) levels in females;[111–113] however, many member institutions utilize these tests for fertility assessment. Unlike FSH, AMH does not need to be drawn on a specific day of the menstrual cycle, and is minimally influenced by hormone therapy. When applying these guidelines to a large cohort of adult survivors of childhood cancer (median age 32 years), 11.8 % of females were found to have primary ovarian failure, 11.5% of males had sex hormone deficiency, and 66.4% had an abnormal semen analysis.[114]

Female hormone replacement therapy (HRT) is required to initiate and support breast and uterine development, treat vasomotor and genitourinary symptoms, maintain bone mineral density, and protect against cognitive decline.[115,116] In pre-pubertal patients, low dose estrogen is increased incrementally over 2 years, with progestins (continuously or cyclically) added at 2 years or with breakthrough bleeding, whichever occurs first. Various regimens and routes of administration may be utilized depending on patient preference, and should continue until expected age of menopause, approximately age 52. Transdermal 17β-estradiol provides the most bioavailable delivery of estrogen with equal distribution to all tissues and lesser effect on hepatic proteins and triglycerides.[117] Radiation to the breast may cause hypoplasia or arrested development which may not recover with estrogen therapy.[118,119] In boys, normal puberty frequently occurs due to preserved testosterone production. If puberty does not occur, testosterone can be replaced by injection, patch, or gel. In patients who have not yet attained their final height, HRT should be supervised by pediatric endocrinology to ensure appropriate growth and development.

Contraception

Misinformation regarding fertility after cancer treatment augments unplanned pregnancy risk, making reliable contraception critical.[120] Pregnancies can occur even in patients diagnosed with primary ovarian insufficiency, and have been reported in patients on oral contraceptives.[121,122] As with all female HRT, relevant issues include timing of initiation, thrombotic risk, and risk of breast cancer in patients who received chest irradiation.

Other health consequences

Sexual function can be diminished in cancer survivors, even after adequate hormone replacement, and may require the assistance of specialized sex therapists. Other reproductive health concerns in female cancer survivors include genital graft-versus host disease after transplant and pelvic radiation with risk of vaginal stenosis and obstructive hematocolpos (menstrual blood trapped in vagina).[123,124] Topical immunosuppressive agents are first-line therapies. Prophylactic vaginal dilation may improve outcome; however, surgical intervention may be warranted for refractory cases. Early evaluation of SCT patients minimizes these sequelae.

BARRIERS TO PROGRAM DEVELOPMENT AND UTILIZATION

Establishing a formal fertility program has been consistently shown to increase FP rates and improve patient satisfaction,[8–10,14,125,126] yet PIN members cite multiple barriers to program development and utilization. The most common barriers to establishing a program include: lack of financial/institutional support, inadequate time for program development due to other clinical/academic responsibilities, difficulty obtaining IRB approval for OTC and TTC, and inadequate access to reproductive endocrinology/urology.

Even after a fertility program is established, there may be a number of barriers to utilization —particularly low referral rates.[127–129] Many pediatric providers are not aware of infertility risk and the various FP options, or may have negative opinions of FP, and it is often difficult to identify provider champions from other disciplines.[40,130,131] Raising institutional awareness regarding gonadotoxic therapies can be achieved in many ways, including multi-disciplinary team meetings, staff training, and policy/procedural changes.[17] Including a FP consultation order in order sets or checklists may aid in provider recall and simplify the referral process, thereby increasing referral numbers. “Opt-out” rather than “opt-in” approaches could be considered. Streamlining communication between referring teams and the fertility consult service is important for overall success. Single points of contact with timely responses can dispel concerns, manage acute needs, and increase likelihood of future consultation. An easily accessible and educational program website also aids in referrals.[16]

Even as provider awareness increases, other factors may impact referral rates for fertility counseling and FP utilization in pediatrics, including expense/limited insurance coverage, medical and/or psychological urgency to start treatment, parental (or provider) discomfort discussing reproductive health with children, and challenges with established FP methods (sperm and oocyte cryopreservation) in adolescents due to invasiveness/sexual inexperience.

Other FP options that may be more feasible (such as OTC, TTC, and GnRH analogues) remain experimental.

Fertility teams should be aware of these challenges and develop strategies to provide counseling to all patients at risk for infertility, in addition to trying to facilitate FP completion for interested patients and families. Financial resources should be identified early in program development. Funding may be obtained through federal or foundation grants, team fundraising, or internal hospital support that targets multidisciplinary initiatives with focus on clinical and research expansion. The patient navigator/social worker can identify families with financial need and connect them to philanthropic programs to reduce procedural and storage fees and other associated costs (Table 3).[132] Ultimately, even if costs or other barriers are insurmountable, research has shown that patients and families prefer to have received information about all possible options, even if no option is ultimately pursued.[133]

RESEARCH OPPORTUNITIES

As the field of pediatric FP continues to grow, many clinical, translational, and basic science research questions need to be addressed. The most challenging aspect of FP research is the ability to track and collect long term outcomes in patients who undergo FP interventions. By definition, infertility is a very late onset side effect of therapy which is not diagnosed until 5–30 years after the completion of gonadotoxic therapy. In addition to the ongoing work on OTC and TTC, clinical research opportunities for pediatric FP programs include: evaluating necessary resources to implement OTC/TTC protocols, examining predictors of FP utilization, creating and assessing tools for risk assessment and shared decision making, identifying best surgical techniques for TTC, OTC, and ovarian transposition, and exploring fertility opportunities after gonadotoxic therapy. While sperm banking for postpubertal males is generally low risk, risk/benefit analysis of FP procedures for other groups (females and prepubertal males) should be performed, including individualized gonadal risk assessment and whether it justifies the risk of FP procedures; stimulation and oocyte cryopreservation versus ovarian tissue cryopreservation in adolescents; amount of ovarian tissue needed for pregnancy; whether oophorectomy pre-chemotherapy significantly increases the possibility of achieving pregnancy in the future versus risk of gonadal insufficiency; development of tests to assess for cancer cells in the ovarian tissue; and in which cases OTC should occur after chemotherapy.

Further, while fertility research in pediatric oncology continues to expand, the role of FP in other medical conditions that impact fertility, such as Turner, Klinefelter, other differences of sex development, and transgender individuals, is poorly understood. Additionally, rates of fertility counseling and FP are significantly lower in non-oncologic populations. Consortia such as the PIN provide opportunities to develop multi-site research collaborations, and resources should be allocated to develop protocols and secure funding to answer many of these critical questions.

ETHICAL CONSIDERATIONS

Ethical quandaries exist in pediatric FP, including parental decision-making, child decisional capacity, experimental FP method use, religious issues, and disposition of stored gametes or tissue upon death. Parents have legal authority over most health-related decisions of children under age 18, and parental permission is needed for treatment.[134] The scarce literature on the role of parents in FP decision-making suggests a child's fertility is a "right in trust" to be safeguarded; parents are justified in making decisions for their child.[65,135] Multiple national and international organizations support parental FP decision with child assent (age >7 years).[1,3,12,23,136] Other literature shows discordance between teens and their parents' FP goals.[137–140] Systematic reviews of teen health decision-making show a strong desire to participate in treatment decisions and concerns about future fertility.[141–144] Specialized consent forms need to be developed for the adolescent population, which allow them to assent to procedures.

Ethicists have argued that experimental FP procedures offer hope and an open future while others suggest they are not essential to health, increase medical risk and create financial burden.[65,145–147] It is important to be sensitive to families' views on the use of assisted reproductive technologies, that may be guided by their religious, cultural, or personal beliefs.[148] Finally, disposition of stored gametes from a minor should be discussed with youth capable of assent and agreed upon by the parent(s) prior to collection. Some clinics require destruction of such gametes upon death; others allow the minor to "will" gametes to a relative.[1,3,145,146,149] Ultimately, shared decision making between parent, child and provider may alleviate ethical concerns.[150] Some cases may benefit from input from an ethics committee or medical ethicist.[151]

CONCLUSION

Although fertility was historically thought to be irrelevant to pediatrics, it has become clear that timely discussion about FP, and a dedicated program to facilitate this process, improves outcomes. While practices vary even within the PIN, members agree that a multidisciplinary team and patient navigator are among the most important aspects of a successful program. Many pediatric FP programs are facing major barriers, particularly financial. Referrals for fertility counseling remain inconsistent, and obtaining IRB approval for tissue preservation remains problematic at many centers. There are still multiple research and ethical questions that remain unanswered, and are critical to examine in order to provide optimal counsel. Collaboration between centers is essential to furthering the field and breaking down barriers, in order to provide these vulnerable patients with the reproductive care they need and deserve.

Acknowledgments

Funding Source:

Center for Reproductive Health After Disease (P50HD076188) from the National Institutes of Health National Center for Translational Research in Reproduction and Infertility (NCTRI)

Abbreviations:

FP	fertility preservation
PIN	Pediatric Initiative Network
REI	reproductive endocrinologists
PAG	pediatric and adolescent gynecologists
SCT	stem cell transplantation
DSD	differences of sex development
OTC	ovarian tissue cryopreservation
IRB	Institutional Review Board
TTC	testicular tissue cryopreservation
TESE	testicular sperm extraction
SSCs	spermatogonial stem cells
AMH	anti-Mullerian hormone
HRT	hormone replacement therapy

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Table 1.

Suggested resources to request from institution for optimal program development. Note that the inability to secure these resources does not necessarily preclude establishing an FP program. *Based on historical criteria for Fertile Hope's Center of Excellence designation

Requested Personnel	**Roles and Responsibilities**
Fertility Preservation Program Director (with protected time/effort)	Oversee all aspects of program, including: • Develop referral pathways and local models of care • Create and maintain standard operating procedures for all aspects of FP care • Supervise and educate patient navigator • Develop, maintain, and distribute educational materials for patients and providers • Maintain contractual agreements with organizations that provide financial and logistical assistance to fertility preservation patients (e.g., LiveStrong, ReproTech) • Develop and maintain tissue cryopreservation programs • Secure philanthropic funds to support the program • Meet regularly with stakeholders in other disciplines • Develop a strategy for ethical oversight and review of difficult cases • Ongoing quality improvement
Dedicated Patient Navigator/Coordinator	• Serve as the primary point of contact for the program • Receive initial call from referring team (e.g. oncology) • Obtain patient and referring provider contact information • Notify gynecology or urology team of consult as needed • Schedule fertility preservation consults within 24–72 hours depending on disease process • Contact Reproductive Endocrinology and Infertility (REI) to arrange assisted reproductive technologies, if selected • Coordinate appointments, referrals, testing and procedures. • Consent and enroll subjects in research studies in coordination with research coordinator. • Remain a central point of contact for the patient and family • Provide resources to patients and parents/partners • Provide decisional support • Identify fertility-related distress and refer to appropriate support services • Arrange follow-up visits at end of therapy, 6 months, 12 months and yearly, or as indicated per specialty • Serve as a liaison between the program, the institution and the community • Maintain database of all patients evaluated for fertility preservation and provide follow-up of research studies in coordination with research coordinator
Requested Facilities	**Functions Served**
Clinic Space	• Outpatient fertility preservation consults in an age-appropriate space • Availability to allow for patients to be seen with 48 hours* of consult being placed
Laboratory Space	• Pathology assessment of ovarian or testicular tissue

	• Tissue processing and storage • Tissue Shipping • Maintain appropriate lab accreditation
Embryology/Andrology Space (or access to an offsite center)	• Sperm cryopreservation • Oocyte/embryo cryopreservation • Maintain appropriate lab accreditation

Table 2.

List of key stakeholders for an ideal FP team, along with potential roles each member can fulfill in an FP program. Availability and engagement of these team members will vary by institution.

Key Stakeholders/Team Members	Potential Roles and Responsibilities
Pediatric Oncology	• Primary provider for subset of patients • Risk stratification and counseling • Communication of treatment plan and urgency, patient prognosis • Provide appropriate reproductive referrals during and after cancer treatment • Identify fertility related distress in patients or parents and make appropriate referral
Pediatric Endocrinology	• Primary provider for subset of patients • Risk stratification and counseling • Hormone replacement therapy (male and female) • Management of complications of hormonal failure • Pubertal development (male and female)
Pediatric Surgery	• Surgical preservation procedures (OTC/TTC/oophoropexy) • Combining procedures with standard of care surgeries
Pediatric and Adolescent Gynecology	• Risk stratification and counseling • Surgical preservation procedures (OTC/oophoropexy) • Hormone replacement therapy (female) • Pubertal development (female) • Gynecologic care • Reproductive needs in survivorship
Reproductive Endocrinology and Infertility	• Risk stratification and counseling • Surgical preservation procedures (OTC) • Assisted Reproductive Technology (oocyte/embryo cryopreservation) • Hormone replacement therapy (female) • Reproductive needs in survivorship
Pediatric Urology/Andrology	• Risk stratification and counseling • Surgical preservation procedures (TTC) • Sperm extraction procedures • Counsel about abnormal semen parameters • Urologic Care • Reproductive needs in survivorship
Non-oncologic Medical (e.g., Rheumatology, Hematology, Pulmonary, Immunology)	• Primary provider for subset of patients • Communication of treatment plan and urgency, patient prognosis • Partnership for non-oncologic FP expansion
Pathology	• Pathologic tissue evaluation

Key Stakeholders/Team Members	Potential Roles and Responsibilities
	• Determine tissue processing protocols & logistics
Fertility-Trained Mental Health Professionals/Child Life	• Provide support to both the patient and family in making fertility preservation decisions • Help patients work through potential loss of fertility
Ethics	• Advise team in cases with ethical uncertainty
Genetics	• Counsel patients with heritable conditions about risk to offspring

Table 3.

Philanthropic organizations to assist fertility preservation programs and/or patients.

Research	**Financial Assistance/Funds**
Bear Necessities	Children's Miracle Network
American Cancer Society	Livestrong Sharing Hope
St. Baldrick's Foundation	Fertile Action
Alex's Lemonade Stand	Fertility Within Reach
Pediatric Oncofertility Research Foundation	Walgreen's Heartbeat Program
	Verna's Purse (tissue storage through Reprotech)