Review Article

Fertility Preservation Options in Pediatric and Adolescent Patients With Cancer

Karen C. Burns, MD[1]; Holly Hoefgen, MD[2]; Andrew Strine, MD[3]; and Roshni Dasgupta, MD, MPH[4]

Abstract: The incidence of childhood cancer has steadily increased since the 1950s, with approximately 16,000 children diagnosed each year. However, with the advent of more effective multimodal therapies, childhood cancer survival rates have continued to improve over the past 40 years, with >80% of patients now surviving into adulthood. Fertility preservation (FP) has become an important quality-of-life issue for many survivors of childhood cancer. As a result, the therapeutic options have become less gonadotoxic over time and more patients are being offered FP options. This review examines the indications for consultation, male and female FP options both in the prepubertal patient and adolescent patient, and the unique ethical issues surrounding FP in this vulnerable population. ***Cancer*** **2018;124:1867-76**. *© 2018 American Cancer Society.*

KEYWORDS: adolescent, fertility preservation, oncofertility, pediatric, pediatric oncology, surgery.

INTRODUCTION

The incidence of childhood cancer has steadily increased since the 1950s. The current incidence is estimated to be approximately 17 per 100,000 children living in the United States. In 2016, approximately 15,700 children in the United States were diagnosed with a malignancy.[1] Fortunately, childhood cancer survival rates have continued to improve over the past 40 years. Current estimates of 5-year overall survival for childhood cancer exceed 83%, with modern-era survivors living well into adulthood.[2] As this population continues to age and increase in number, our knowledge of late effects continues to grow. Even with risk-adapted therapy, the aggressive treatment regimens that have achieved these improved survival outcomes come at a clear cost. Cancer survivors are at risk of complications (late effects) from their cancer and/or cancer therapy throughout their lifetime. The St. Jude Lifetime Cohort Study recently demonstrated that as many as 99.9% of childhood cancer survivors have at least one National Cancer Institute Common Terminology Criteria for Adverse Events-graded late effect as a result of their cancer itself or the cancer-directed therapy.[3] These late effects include gonadotoxicity with the potential for permanent azoospermia or premature ovarian insufficiency in survivorship.

Oncology Perspective

Many patients report a reliance on their primary oncologist to discuss the issues of gonadotoxicity and fertility preservation (FP).[4] FP has been addressed by multiple large medical organizations that have issued consensus statements regarding the importance of FP at the time of diagnosis and throughout survivorship. The American Society of Clinical Oncology first published guidelines in 2006 and most recently updated their statement in 2013.[5] The updated guidelines emphasize the importance of addressing gonadotoxicity and FP in all patients with reproductive potential, including the pediatric population.

Early conversations are essential to maximize the number of available FP options available to the patient, and should be initiated at the time of diagnosis.[5] The American Society for Reproductive Medicine similarly emphasized that parents/guardians can act to preserve the fertility of their minor children.[6] Both the American Society of Clinical Oncology and the American Society for Reproductive Medicine stressed the need to refer to subspecialists for procedures not available at the home institution.

Corresponding author: Roshni Dasgupta, MD, MPH, Division of Pediatric General and Thoracic Surgery, Cincinnati Children's Hospital Medical Center, University of Cincinnati, 3333 Burnet Ave, Cincinnati, OH 45229; roshni.dasgupta@cchmc.org

[1]Cancer and Blood Disease Institute, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio; [2]Division of Pediatric and Adolescent Gynecology, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio; [3]Division of Pediatric Urology, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio; [4]Division of Pediatric General and Thoracic Surgery, Cincinnati Children's Hospital Medical Center, University of Cincinnati, Cincinnati, Ohio.

The first 2 authors contributed equally to this article.

We thank the LiveWell Collaborative and Mr. Brycen Ferrara for the artwork.

DOI: 10.1002/cncr.31255, **Received:** November 15, 2017; **Revised:** December 13, 2017; **Accepted:** December 15, 2017, **Published online** January 25, 2018 in Wiley Online Library (wileyonlinelibrary.com)

Despite these guidelines, many primary oncologists are uncomfortable or feel ill-equipped to provide adequate counseling to patients with cancer and/or survivors.[7] Banerjee and Tsiapali reported that <50% of patients recalled discussing fertility risks with their health care provider at the time of diagnosis.[8] Even fewer oncologists report discussing FP with their patients.[9]

Risk of Gonadotoxicity

The risk of gonadotoxicity has been well established with increasing cumulative doses of chemotherapy with alkylating agents as well as direct radiotherapy to the gonads.[10] Risk is commonly classified as low (<20% experience infertility), intermediate (21%-80% experience infertility), or high (>80% experience infertility). Males are at sustained risk at all ages, whereas prepubertal females are relatively protected from the gonadotoxic effects of chemotherapy. Green et al developed the cyclophosphamide equivalent dosing score to standardize cumulative dosing across protocols using various alkylating agents via a mathematical calculation; this score allows risk to be assigned to a given treatment regimen.[11] Even with the standardization of the alkylating agent dose, a significant degree of interpatient variability still exists. The St. Jude Lifetime Cohort Study was able to demonstrate that although the risk of gonadotoxicity increases with increasing cumulative dose, there is no lower limit of dosing below which one is considered "safe" from the risk of infertility. Likewise, several survivors who received a cumulative dose above the high-risk threshold have maintained fertility, suggesting that not all patients are affected equally, even at high doses. This again underscores the need for comprehensive patient education regardless of risk.[12]

Radiotherapy also is implicated in infertility because both the ovaries and testes are exquisitely sensitive to the harmful effects of radiation and there is the potential for permanent infertility at relatively low doses. In prepubertal male patients, a dose of 6 grays (Gy) to the testis can result in permanent azoospermia, whereas in adult men the threshold is lowered to 2.5 Gy. Ovarian function is similarly affected by low doses of radiation when the ovaries are directly within the radiation field. In prepubertal females, a dose of >15 Gy has been implicated in infertility. This threshold is lowered to >10 Gy in postpubertal female patients and >6 Gy in adult women. Female patients also are at risk from craniospinal radiation doses >24 Gy due to the radiation scatter to the ovaries. Cranial/brain irradiation >40 Gy may result in gonadotropin deficiency and subsequent amenorrhea.[13]

Both male and female patients undergoing bone marrow transplantation frequently are at high risk of infertility, regardless of age, due to the conditioning regimens used in the myeloablation process.[13] High doses of alkylating agents (cyclophosphamide, busulfan, or melphalan) are common, with or without total body irradiation. Reduced intensity conditioning regimens may decrease the risk of late effects, but to the best of our knowledge there is insufficient evidence to determine whether this results in a lower incidence of gonadal failure after transplantation, and therefore at our institution reduced intensity conditioning still is considered to be high risk.

Timing of the FP Consultation

The topic of gonadotoxicity and FP is complex and best discussed early in the diagnostic process to allow the patient and his or her family the widest array of options. However, this also is an emotional and overwhelming time for most families. Several medical disciplines have used decision aids, both written and visual, to help with engaging families in a shared decision-making process to decrease their decisional regret.[14] Decision aids may prove to be a useful tool in oncofertility as well. Patients and families should be given an individualized assessment of gonadotoxic risk and information regarding FP as early as possible in the diagnostic process. This will allow time for a decision regarding FP to be made and procedures to be completed prior to the initiation of therapy. The concept of FP should be carried through to (and beyond) survivorship.[5,6] Because many female patients will have a shortened window of fertility after therapy, continued education and discussion of FP options is important in this setting.

Multidisciplinary Team Approach

To aid in discussions regarding fertility risks and FP options, many pediatric and adolescent and young adult (AYA) institutions are developing FP teams or services. The number of both fertility consultations and FP procedures increase with on-site fertility expertise, personnel, and services.[15,16] These teams generally are comprised of multidisciplinary members charged with providing patient education as well as the coordination of FP procedures. A pediatric/AYA fertility team may include a combination of pediatric oncology, adolescent gynecology, pediatric urology, pediatric surgery, reproductive endocrinology, social work, genetics, and psychology based on institutional practice and the availability of personnel. A fertility patient navigator is extremely beneficial to a

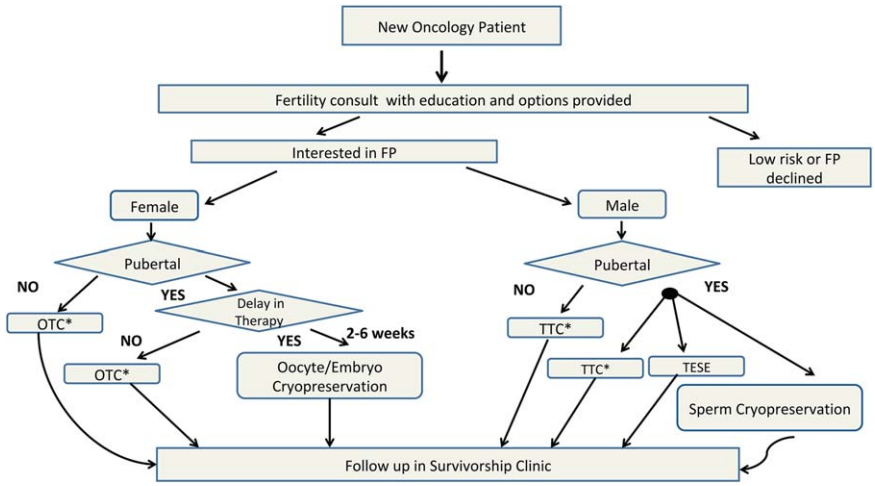

Figure 1. Fertility consultation flow diagram. FP indicates fertility preservation; OTC, ovarian tissue cryopreservation; TESE, testicular sperm extraction; TTC, testicular tissue cryopreservation. *Indicates an experimental procedure performed only under institutional review board approval; patient must meet inclusion/exclusion criteria.

TABLE 1. Fertility Preservation Techniques and Success Rates

Preservation Technique	Clinical Pregnancy Rate
Males	
Sperm cryopreservation	23%-57%
Testicular tissue cryopreservation	No human pregnancies
Females	
Oocyte cryopreservation	4%-12% per oocyte (36%-61% clinical pregnancy rate per subsequent embryo transfer)
Embryo cryopreservation	36%-61%
Ovarian tissue cryopreservation	57.5%[a]

[a] Based on a single meta-analysis (remains experimental).

comprehensive team approach, providing a single point of contact for patients, families, and consulting teams. Institutions with open research protocols also may benefit from having a research coordinator and member of pathology on the fertility team.[17]

We strongly recommend that all patients are offered fertility consultation regardless of infertility risk or eligibility for FP options to ensure standardized education and access (Fig. 1). Successful pregnancy rates with each type of procedure also should be discussed with the patient and the family (Table 1). Patients with a change in therapy leading to a change in gonadotoxicity risk should be reevaluated by the fertility team. Fertility education and monitoring then should be continued through the survivorship process to meet the changing needs of each patient.[5]

Female FP

Females are born with a finite oocyte reserve that is slowly depleted over time until the age of natural menopause. Cancer-directed therapy can cause a depletion of this reserve with variable risk as discussed above. FP options available to female patients often are more invasive and time-consuming compared with those for male patients. Therefore, the options chosen may be based not only on age and pubertal status, but also on the timing of oncologic therapy. Established options include oocyte/embryo cryopreservation as well as ovarian transposition and shielding from radiation. Ovarian tissue cryopreservation (OTC) is available at select institutions under institutional review board protocol only. Gonadotropin-releasing hormone analogues for ovarian suppression are commonly considered, but to our knowledge the effectiveness data are mixed, demonstrating no effectiveness in several populations including most pediatric and AYA-associated cancers. Its use should be considered experimental for FP and limited to institutional review board-approved protocols in this population.[5,18,19]

Oocyte and embryo cryopreservation

For postpubertal patients, embryo cryopreservation with oocyte cryopreservation has been the standard of care since 2012 as per the American Society for Reproductive Medicine.[20] This relieves the barrier for the current use of sperm, leaving the choice of partner or donor for the patient's future. Both methods begin with medical ovarian stimulation (via multiple hormonal injections), follicular monitoring using ultrasound (standardly via a

transvaginal approach), and subsequent transvaginal oocyte retrieval under sedation or anesthesia. The process creates unique barriers specific to pediatric and adolescent patients who may not have had previous intercourse or vaginal procedures, and often are more emotionally immature. The use of adolescent-friendly protocols with smaller ultrasound probes and/or limited vaginal procedures can be helpful. After retrieval, oocytes then are either directly cryopreserved or can be matured, fertilized in vitro with donor or partner sperm, and then cryopreserved as embryos. The eventual use of cryopreserved oocytes/embryos will require in vitro fertilization (IVF). Clinical pregnancy rates (CPRs) per oocyte nationally range from 4% to 12%, with a CPR of 36% to 61% per subsequent embryo transfer, similar to that of fresh oocytes and fresh/frozen embryos (Fig. 2).

Concerns regarding delays in therapy have been one of the greatest barriers to the use of FP options in general and can be especially complicated in pediatric cancers, which often require the urgent initiation of treatment. However, luteal-phase and random-start controlled ovarian stimulation protocols can result in a time from consultation to cryopreservation of as little as 2 weeks. It is important to work closely with the primary oncology team to weigh the risks and benefits on a case-by-case basis to determine whether standard-of-care options for FP can be made available.

Ovarian tissue cryopreservation

To the best of our knowledge, OTC is the only FP option for prepubertal females and for postpubertal patients who are unable to delay the initiation of chemotherapeutic treatment. Laparoscopic unilateral oophorectomy (partial or complete) is the preferred surgical technique. OTC has been completed in patients of all ages, and has been shown to be safe and effective with low complication rates with minimal to no delays in therapy.[21,22] Recent studies also have demonstrated the effectiveness of the technique in patients who have previously undergone chemotherapy, opening FP options to select patients between cycles and after treatment.[23] This becomes especially important for patients initially treated with agents with low gonadotoxic risk, in whom disease progression alters treatment to agents with higher gonadotoxic risk.

At the time of removal, ovarian tissue is evaluated for macroscopic evidence of malignant disease. The ovarian cortex, which contains the primordial follicles, is separated from the medulla and dissected into 1-mm to 2-mm thick strips for cryopreservation.[24] Although slow-freeze techniques for cryopreservation currently are the standard, initial data from more recent studies have shown vitrification (rapid freeze) to be at least comparable if not favored. More data are needed because the majority of reproductive centers currently use vitrification techniques for oocyte/embryo cryopreservation and may more easily integrate OTC with similar processing.[20] Studies also have demonstrated successful pregnancies in patients with ovarian tissue specimens that were transported overnight (up to 20 hours) prior to cryopreservation.[25]

Ovarian tissue transplantation (OTT) is the process of thawing and then surgically returning the ovarian cortical strips to patients. Techniques described include transplantation to orthotropic (ovarian fossa, contralateral ovary, or pelvic side wall) or heterotopic (subcutaneous areas of the forearm or retroperitoneal space under the abdominal wall) locations.[21,23,25-27] To the best of our knowledge, all live births to date have used orthotopic transplantation without specific data available regarding the ideal orthotopic location.[21] To our knowledge, to date there have been >130 live births and several ongoing pregnancies from OTT, mostly from patients who were adult women at the time of cryopreservation.[21,28] There are 2 reports of live births in patients who underwent OTC prior to menarche with subsequent OTT (one of whom was peripubertal and one who was prepubertal), indicating promise for its use in this population.[29,30] After OTT, there is variable use of additional assisted reproductive techniques (ARTs), with live births documented with and without the use of IVF.[23,25,26,29] A recent meta-analysis has suggested a CPR of 57.5% and a live birth rate of 37% after OTT.[21] Fetal anomalies (1%-2%) and perinatal outcomes are similar to those of the general population.[27,31]

Because OTT is the only FP option to restore hormonal function in females, it is important to review the endocrine function restoration rate of 63% noted in meta-analysis.[21] However, the longevity of the graft is quite variable and averages only 2 to 5 years, demonstrating that the technique currently should be used only at the time pregnancy is desired.[21,26] To our knowledge, the exact cause of this longevity concern is unknown, but could be multifactorial (eg, age, chemotherapy history, cryopreservation and transplantation techniques, or amount of tissue replaced). Recent studies have suggested that the ischemic phase after transplantation is likely more significant for follicular loss than freezing/thawing techniques.[21] Areas for improvement in OTT could include the addition of agents to enhance vascularization or the extracellular matrix scaffold.[21,27]

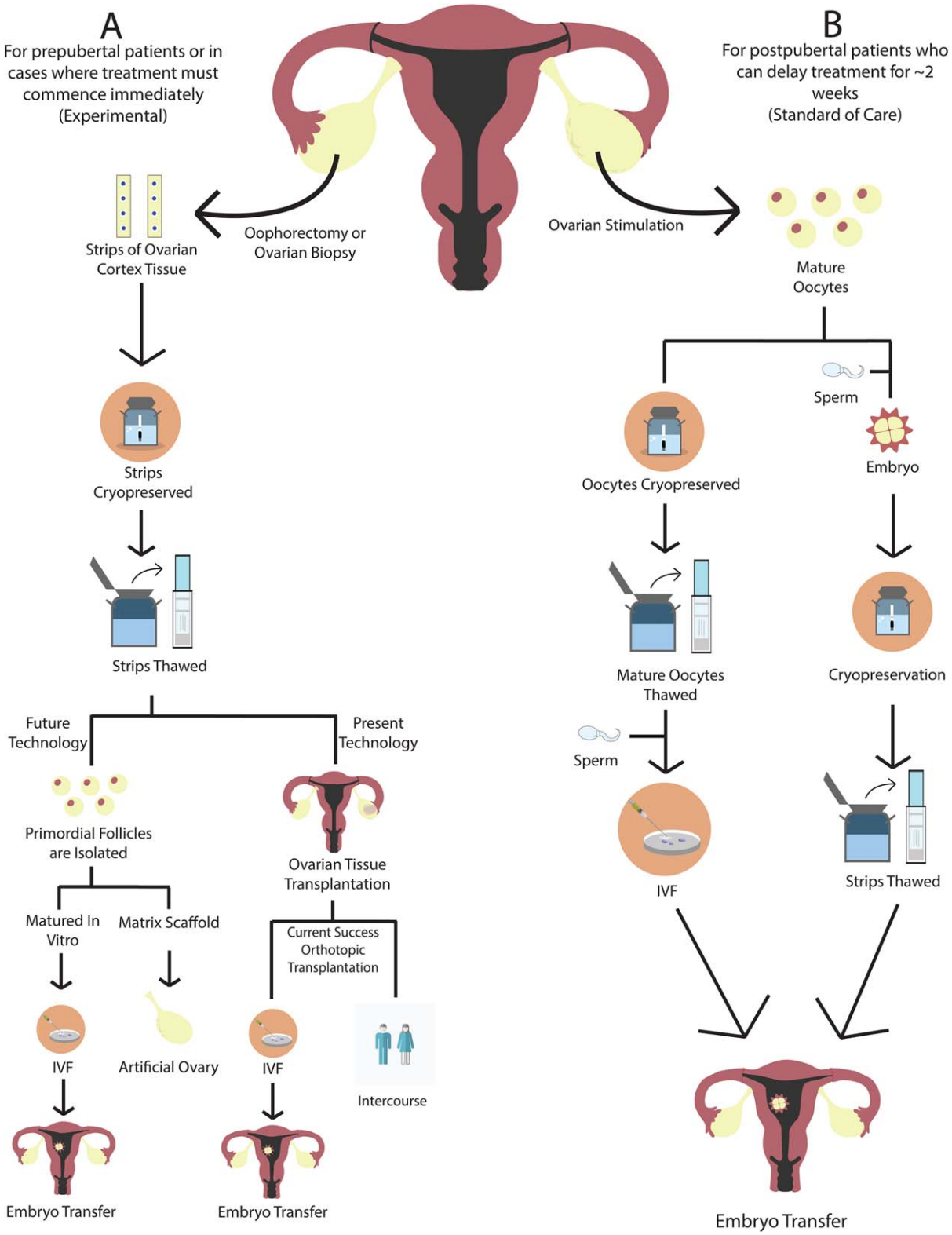

Figure 2. Female options for fertility preservation. (A) For prepubertal girls and postpubertal females who cannot delay treatment, ovarian tissue can be removed (multiple biopsies vs whole ovary) and cut into thin cortical strips under an experimental protocol. The tissue then is cryopreserved. At the time of desired fertility, the tissue is thawed and transplanted back into the patient (if a minimal risk of malignancy transfer is assured). Current pregnancies are achieved via orthotopic (ovarian fossa, contralateral ovary, or pelvic side wall) transplantation. Patients may attempt intercourse or use assisted reproductive techniques to achieve pregnancy. Future techniques currently are being explored for patients in whom the risk of malignant transfer cannot be assured. These include the isolation of oocytes from ovarian tissue followed by in vitro maturation and in vitro fertilization (IVF), as well as the creation of an "artificial ovary," in which primordial follicles are transferred to a matrix scaffold. These techniques have noted live births in animal models only. (B) Postpubertal females who can delay treatment for $\geq$2 weeks can undergo ovarian stimulation followed by the removal of mature oocytes. Oocytes then are either directly cryopreserved or fertilized in vitro with donor or partner sperm and cryopreserved as embryos. The eventual use of cryopreserved oocytes/embryos will require IVF.

There is a legitimate concern for oncologic reseeding in patients with higher risk tumors, such as ovarian and blood-born malignancies, as well as in patients at risk of ovarian metastases. Ongoing research into techniques of in vitro maturation to isolate and mature oocytes from the removed ovarian cortical tissue either at the time of ovarian harvest and/or at the time of thawing cryopreserved tissue is promising. This technique may mitigate the risk of oncologic reseeding. Although to our knowledge there have been no live births reported with these techniques, encouraging results have been noted in several murine models.[32] Further research also currently is ongoing to create an "artificial ovary," in which primordial follicles are transferred to a matrix scaffold, therefore eliminating the risk of transmitting malignant cells, with success noted in mice models.[28,33] In addition, a study by Meirow et al included 2 patients with leukemia who were considered to be at high risk of ovarian involvement. Both patients received chemotherapy prior to OTC and cortical strips then were extensively screened for seeding prior to OTT; neither patient had developed disease recurrence at 1 to 5 years of follow-up and one patient had conceived. The authors stress that although there is never a guarantee of disease-free tissue, these initial data suggest that OTC/OTT can be offered to a select group of patients with leukemia.[23]

The birth rates and safety data are based on relatively small numbers, but are similar to rates described for oocyte cryopreservation. It is suggested that OTC/OTT merit consideration as the standard of care.[21,28]

Male FP

A variety of options exist for FP in male children and adolescents with cancer, including gonadal shielding, sperm cryopreservation, testicular sperm extraction (TESE), and testicular tissue cryopreservation (TTC).

Sperm cryopreservation

Sperm cryopreservation is the most established option for FP.[5] The updated American Society of Clinical Oncology guidelines recommend that it be offered to all postpubertal patients with a recent diagnosis of cancer.[5] An ejaculated semen specimen typically is obtained by masturbation, but also can be obtained by penile vibratory stimulation or electroejaculation in patients who cannot perform masturbation. Electroejaculation must be performed under general anesthesia.[34-39]

The optimal timing for sperm cryopreservation is prior to the initiation of therapy because the quality of the semen specimen and DNA integrity may be compromised even after a single course of chemotherapy.[5] In a retrospective cohort study of semen parameters for a large cohort of adolescents and young adults with cancer, approximately 84.0% of patients who provided a semen specimen after the initiation of treatment were azoospermic, compared with only 16.9% in untreated patients.[40] Despite this recommendation, an inadequate duration of time between the diagnosis and initiation of therapy often is perceived as a barrier to sperm cryopreservation.[41-43] It certainly can be challenging but should be feasible in a majority of patients, regardless of their clinical state at the time of diagnosis. Several centers have been successful with sperm cryopreservation in >80% of adolescents and young adults prior to the initiation of therapy. Studies have emphasized the importance of offering sperm cryopreservation to all adolescents, regardless of their underlying diagnosis or risk of gonadotoxicity with the planned treatment.[40,44]

To the best of our knowledge, the age at which to offer sperm cryopreservation is unclear. An improvement in various semen parameters has been reported with increasing age, including the volume, concentration, total motile count, and rate of azoospermia.[38,40,45,46] However, an adequate semen specimen can be obtained in adolescents as young as 11 years of age.[40] Sperm cryopreservation has been successful in up to 64.5% of adolescents aged 11 to 14 years, with their semen parameters comparing favorably with the World Health Organization reference values for fertile adult men.[40,47] The stage of pubertal development is considered a better predictor of spermarche, although a wide variation in testicular size and the presence of secondary sexual characteristics still can be present at its onset. Sperm cryopreservation generally is offered to adolescents who are at least Tanner stage 3 in their pubertal development.[40,44]

To our knowledge, there are no guidelines currently available regarding the quality of cryopreserved semen and its duration of storage for FP. Although many patients with cancer have abnormal semen parameters at the time of cryopreservation, only a small number of viable sperm are needed for ART. CPRs with cryopreserved sperm range from 23% to 57% for this population, which is similar to those for standard IVF/intracytoplasmic sperm injection for infertile couples.[44] The rate of fetal anomalies and perinatal outcomes are similar to those of the general population as well.[44]

Testicular sperm extraction

TESE is a procedure that involves the direct retrieval of sperm from the testis for ART in patients with

azoospermia. The use of an operating microscope with microsurgical TESE can assist further in the identification of focal areas of spermatogenesis in the seminiferous tubules. TESE is well tolerated, with a short convalescence and a low risk of minor complications, including scrotal hematoma, infection, persistent pain, and swelling. The risk of testicular damage is low but more commonly occurs within the setting of multiple biopsies without a microsurgical technique.[48] TESE has become an emerging option for patients with cancer and has been termed onco-TESE.[49] Sperm retrieval has been successful in 47% and 37% to 65% of patients prior to and after the initiation of chemotherapy, respectively.[35,44,49] To our knowledge, only 1 study to date included AYA patients and noted a 0% sperm retrieval rate for patients with Tanner stage 2, 44% for those with Tanner stage 3, 80% for those with Tanner stage 4, and 69% for patients with Tanner stage 5 pubertal development.[35]

Testicular tissue cryopreservation

The options for FP are limited prior to the onset of puberty due to a lack of mature sperm. TTC is experimental, but currently has the greatest potential for FP in prepubertal children and adolescents. TTC involves the harvesting of testicular tissue through a transscrotal excisional biopsy and cryopreservation with slow freezing techniques. Eligibility for TTC varies based on the investigational protocol, but generally includes prepubertal children and adolescents at high risk of permanent azoospermia as well as postpubertal adolescents and young adults who are unable to provide a semen specimen. TTC is well tolerated, with minimal postoperative morbidity and no delay in the initiation of therapy.[50-52] Although to our knowledge the long-term effects of TTC on the remaining testis are unknown, the absence of testicular damage and antisperm antibodies in the long-term follow-up of cryptorchid children who underwent a testicular biopsy with an orchidopexy is reassuring.[53]

To our knowledge, no retrieval of mature sperm or achievement of pregnancy has been reported to date. TTC relies on the future development of experimental techniques for the maturation of spermatogonial stem cells (SSCs) into sperm. Several experimental techniques have been described, including the transplantation of SSCs into the testis, de novo testicular morphogenesis with the introduction of SSCs and supporting cells into a decellularized testicular scaffold, autologous grafting and xenografting of testicular tissue, and maturation of testicular tissue in culture.[54] The transplantation of SSCs into the testis would allow for a restoration of natural fertility, whereas the remaining techniques would require the retrieval of mature sperm and ART with IVF/intracytoplasmic sperm injection (Fig. 3).[54] These results have been promising in animal models, but require further validation and translation into human studies. Additional research also is needed regarding the optimization of protocols for cryopreservation and strategies to minimize the risk of disease recurrence from the reintroduction of cancerous cells in the cryopreserved testicular tissue.[44] Given its investigational nature, TTC should be discussed within the context of an institutional board review-approved study.

Issues Specific to Pediatric/AYA Patients

Several ethical concerns may arise that are specific to FP in the pediatric population. These include the right of parental decision making, the child's decisional capacity and right to assent, and what to do if these are at odds. Other concerns include the use of experimental FP procedures in minors, religious concerns regarding FP, and the disposition of stored tissue and gametes at the time of death (which may be increasingly complicated in minors).[55] Consultation with a medical ethicist or their inclusion on the fertility team often is very helpful.

Research has shown that both survivors of childhood and young adult cancer are interested in discussing FP. Although future fertility is not always the main source of concern at the time of the initial diagnosis, it causes considerable stress for both parents and patients once therapy is complete.[4] Letourneau et al demonstrated that female survivors were interested in gaining knowledge regarding the gonadotoxic effects of their cancer treatment.[56] When FP counseling was performed, these patients indicated more satisfaction and less decisional regret regardless of whether they chose to pursue FP.[56] A majority of families are willing to consider and able to make an informed decision concerning FP options, despite the often limited and stressful time prior to the initiation of treatment.[50,51,57] The investigational nature of some options was not perceived as a major deterrent, regardless of whether families ultimately decided to pursue FP or declined.[50,51]

Provider bias has been identified as a potential barrier due to a discordance between the desire of parents and patients for informed decision making and the willingness of providers to offer experimental procedures. Providers are reported to be less willing to offer FP to patients with a low potential for fertility and/or cure, to families with a lower socioeconomic status, and at hospitals that do not have the capability to perform experimental FP procedures.[57]

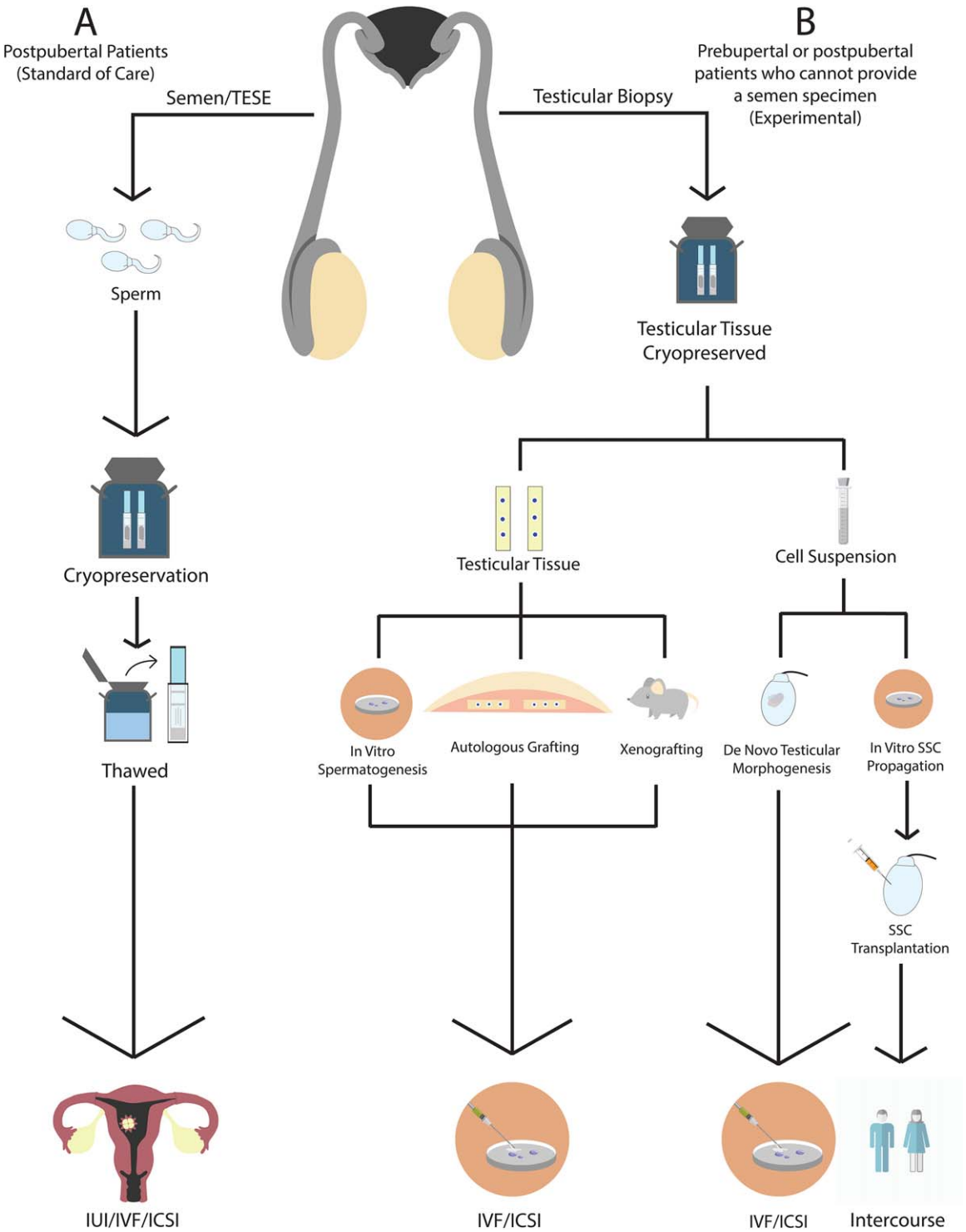

Figure 3. Options for male fertility preservation. (A) An ejaculated semen specimen or testicular sperm extraction (TESE) obtained in postpubertal patients and used for intrauterine insemination (IUI) or in vitro fertilization/intracytoplasmic sperm injection (IVF/ICSI). (B) Testicular tissue containing spermatogonial stem cells (SSCs) can be obtained via biopsy in prepubertal patients and in patients who are unable to provide a semen specimen. SSCs can be expanded in vitro and transplanted back into the testis to restore the potential for natural fertility. A heterogeneous cell suspension of SSCs and supporting cells may undergo de novo testicular morphogenesis by introduction into a testicular scaffold. Intact testicular tissue can be matured in vitro and grafted or xenografted into the scrotum or under the skin. All these techniques are experimental, and all except for SSC transplantation require the retrieval of sperm and IVF/ICSI to achieve pregnancy.

The cost of FP techniques can be significant, and often serves as a barrier for patients and families interested in FP. Many techniques remain experimental and therefore are not covered by insurance. Whenever possible, these techniques should be bundled with other medically necessary surgical procedures to limit anesthetic exposure, minimize cost, and expedite the initiation of therapy. It also is important to connect families with national and institutional philanthropic programs that reduce tissue storage/transfer fees and provide discounted or no-cost medications to patients. Local and institutional philanthropic activities also may provide additional funds that programs may use to offset the costs for patients and families.

Exact costs vary by institution, insurance carrier, and individual fertility coverage. Patients who may have insurance coverage for fertility treatments often are unable to use their benefits because they fail to meet the current definitions of "infertility" that rely on 6 to 12 months of attempted conception without pregnancy.[55] Several states now have introduced bills that would mandate coverage for FP procedures for those patients facing potential infertility as a result of medical treatment. In 2017, bills in Connecticut and Rhode Island were signed into law.[58]

As more patients become survivors of pediatric and AYA cancer, FP will continue to gain importance as an issue that must be addressed both at the time of diagnosis and throughout survivorship. This will best be addressed with a multidisciplinary, patient-centered approach.

FUNDING SUPPORT

No specific funding was disclosed.

CONFLICT OF INTEREST DISCLOSURES

The authors made no disclosures.

REFERENCES

1. CureSearch. Childhood cancer statistics. https://curesearch.org/Childhood-Cancer-Statistics. Access date.
2. National Cancer Institute. Cancer in children and adolescents. https://www.cancer.gov/types/childhood-cancers/child-adolescent-cancers-fact-sheet 2017. Access date.
3. Bhakta N, Liu Q, Ness KK, et al. The cumulative burden of surviving childhood cancer: an initial report from the St Jude Lifetime Cohort Study (SJLIFE). *Lancet.* 2017;390:2569-2582.
4. Stein DM, Victorson DE, Choy JT, et al. Fertility preservation preferences and perspectives among adult male survivors of pediatric cancer and their parents. *J Adolesc Young Adult Oncol.* 2014;3:75-82.
5. Loren AW, Mangu PB, Beck LN, et al; American Society of Clinical Oncology. Fertility preservation for patients with cancer: American Society of Clinical Oncology clinical practice guideline update. *J Clin Oncol.* 2013;31:2500-2510.
6. Practice Committee of American Society for Reproductive Medicine. Fertility preservation in patients undergoing gonadotoxic therapy or gonadectomy: a committee opinion. *Fertil Steril.* 2013;100:1214-1223.
7. Adams E, Hill E, Watson E. Fertility preservation in cancer survivors: a national survey of oncologists' current knowledge, practice and attitudes. *Br J Cancer.* 2013;108:1602-1615.
8. Banerjee R, Tsiapali E. Occurrence and recall rates of fertility discussions with young breast cancer patients. *Support Care Cancer.* 2016;24:163-171.
9. Quinn GP, Vadaparampil ST, Lee JH, et al. Physician referral for fertility preservation in oncology patients: a national study of practice behaviors. *J Clin Oncol.* 2009;27:5952-5957.
10. Ginsberg JP. New advances in fertility preservation for pediatric cancer patients. *Curr Opin Pediatr.* 2011;23:9-13.
11. Green DM, Nolan VG, Goodman PJ, et al. The cyclophosphamide equivalent dose as an approach for quantifying alkylating agent exposure: a report from the Childhood Cancer Survivor Study. *Pediatr Blood Cancer.* 2014;61:53-67.
12. Green DM, Liu W, Kutteh WH, et al. Cumulative alkylating agent exposure and semen parameters in adult survivors of childhood cancer: a report from the St Jude Lifetime Cohort Study. *Lancet Oncol.* 2014;15:1215-1223.
13. LiveStrong. Fertility risk tool. https://www.teamlivestrong.org/we-can-help/fertility-services/risks/. Access date.
14. Rehman B. Shared decision making and the use of patient decision aids. *Perscriber.* 2016;27:33-35.
15. Sheth KR, Sharma V, Helfand BT, et al. Improved fertility preservation care for male patients with cancer after establishment of formalized oncofertility program. *J Urol.* 2012;187:979-986.
16. Peavey M, Arian S, Gibbons W, Lu K, Gershenson D, Woodard T. On-site fertility preservation services for adolescents and young adults in a comprehensive cancer center. *J Adolesc Young Adult Oncol.* 2017;6:229-234.
17. Burns KC, Breech L. Setting up a pediatric oncofertility practice. In: Woodruff TK, Gosiengfiao YC, eds. Pediatric and Adolescent Oncofertility Best Practices and Emerging Technologies. Cham, Switzerland: Springer International Publishing AG; 2017:231-241.
18. Demeestere I, Brice P, Peccatori FA, et al. No evidence for the benefit of gonadotropin-releasing hormone agonist in preserving ovarian function and fertility in lymphoma survivors treated with chemotherapy: final long-term report of a prospective randomized trial. *J Clin Oncol.* 2016;34:2568-2574.
19. Moore HC, Unger JM, Phillips KA, et al; POEMS/S0230 Investigators. Goserelin for ovarian protection during breast-cancer adjuvant chemotherapy. *N Engl J Med.* 2015;372:923-932.
20. Practice Committees of American Society for Reproductive Medicine; Society for Assisted Reproductive Technology. Mature oocyte cryopreservation: a guideline. *Fertil Steril.* 2013;99:37-43.
21. Pacheco F, Oktay K. Current success and efficiency of autologous ovarian transplantation: a meta-analysis. *Reprod Sci.* 2017;24:1111-1120.
22. Corkum KS, Laronda MM, Rowell EE. A review of reported surgical techniques in fertility preservation for prepubertal and adolescent females facing a fertility threatening diagnosis or treatment. *Am J Surg.* 2017;214:695-700.
23. Meirow D, Ra'anani H, Shapira M, et al. Transplantations of frozen-thawed ovarian tissue demonstrate high reproductive performance and the need to revise restrictive criteria. *Fertil Steril.* 2016;106:467-474.
24. Oncofertility Consortium, Northwestern University. OTC: updated user manual. https://oncofertility.northwestern.edu/otc-updated-users-manual. Access date.
25. Dittrich R, Hackl J, Lotz L, Hoffmann I, Beckmann MW. Pregnancies and live births after 20 transplantations of cryopreserved ovarian tissue in a single center. *Fertil Steril.* 2015;103:462-468.
26. Donnez J, Dolmans MM, Pellicer A, et al. Restoration of ovarian activity and pregnancy after transplantation of cryopreserved ovarian tissue: a review of 60 cases of reimplantation. *Fertil Steril.* 2013;99:1503-1513.
27. Oktay K, Bedoschi G, Pacheco F, Turan V, Emirdar V. First pregnancies, live birth, and in vitro fertilization outcomes after transplantation of frozen-banked ovarian tissue with a human extracellular matrix scaffold using robot-assisted minimally invasive surgery. *Am J Obstet Gynecol.* 2016;214:94.e1-9.

28. Donnez J, Dolmans MM. Fertility preservation in women. *N Engl J Med.* 2017;377:1657-1665.
29. Demeestere I, Simon P, Dedeken L, et al. Live birth after autograft of ovarian tissue cryopreserved during childhood. *Hum Reprod.* 2015;30:2107-2109.
30. Walsh F. Woman has baby using ovary frozen in childhood. http://www.bbc.com/news/health-38312995. Accessed October 31, 2017.
31. Jensen AK, Macklon KT, Fedder J, Ernst E, Humaidan P, Andersen CY. 86 successful births and 9 ongoing pregnancies worldwide in women transplanted with frozen-thawed ovarian tissue: focus on birth and perinatal outcome in 40 of these children. *J Assist Reprod Genet.* 2017;34:325-336.
32. Practice Committee of American Society for Reproductive Medicine. Ovarian tissue cryopreservation: a committee opinion. *Fertil Steril.* 2014;101:1237-1243.
33. Laronda MM, Rutz AL, Xiao S, et al. A bioprosthetic ovary created using 3D printed microporous scaffolds restores ovarian function in sterilized mice. *Nat Commun.* 2017;8:15261.
34. Adank MC van Dorp W, Smit M, et al. Electroejaculation as a method of fertility preservation in boys diagnosed with cancer: a single-center experience and review of the literature. *Fertil Steril.* 2014;102:199-205.e1.
35. Berookhim BM, Mulhall JP. Outcomes of operative sperm retrieval strategies for fertility preservation among males scheduled to undergo cancer treatment. *Fertil Steril.* 2014;101:805-811.
36. Hagenas I, Jorgensen N, Rechnitzer C, et al. Clinical and biochemical correlates of successful semen collection for cryopreservation from 12-18-year-old patients: a single-center study of 86 adolescents. *Hum Reprod.* 2010;25:2031-2038.
37. Hovav Y, Dan-Goor M, Yaffe H, Almagor M. Electroejaculation before chemotherapy in adolescents and young men with cancer. *Fertil Steril.* 2001;75:811-813.
38. Muller J, Sonksen J, Sommer P, et al. Cryopreservation of semen from pubertal boys with cancer. *Med Pediatr Oncol.* 2000;34:191-194.
39. Schmiegelow ML, Sommer P, Carlsen E, Sonksen JO, Schmiegelow K, Muller JR. Penile vibratory stimulation and electroejaculation before anticancer therapy in two pubertal boys. *J Pediatr Hematol Oncol.* 1998;20:429-430.
40. DiNofia AM, Wang X, Yannekis G, et al. Analysis of semen parameters in a young cohort of cancer patients. *Pediatr Blood Cancer.* 2017;64:381-386.
41. Nahata L, Cohen LE, Yu RN. Barriers to fertility preservation in male adolescents with cancer: it's time for a multidisciplinary approach that includes urologists. *Urology.* 2012;79:1206-1209.
42. Ogle SK, Hobbie WL, Carlson CA, Meadows AT, Reilly MM, Ginsberg JP. Sperm banking for adolescents with cancer. *J Pediatr Oncol Nurs.* 2008;25:97-101.
43. Schover LR, Brey K, Lichtin A, Lipshultz LI, Jeha S. Oncologists' attitudes and practices regarding banking sperm before cancer treatment. *J Clin Oncol.* 2002;20:1890-1897.
44. Picton HM, Wyns C, Anderson RA, et al; ESHRE Task Force On Fertility Preservation In Severe Diseases. A European perspective on testicular tissue cryopreservation for fertility preservation in prepubertal and adolescent boys. *Hum Reprod.* 2015;30:2463-2475.
45. Daudin M, Rives N, Walschaerts M, et al. Sperm cryopreservation in adolescents and young adults with cancer: results of the French national sperm banking network (CECOS). *Fertil Steril.* 2015;103:478-486.e1.
46. Keene DJ, Sajjad Y, Makin G, Cervellione RM. Sperm banking in the United Kingdom is feasible in patients 13 years old or older with cancer. *J Urol.* 2012;188:594-597.
47. Cooper TG, Noonan E, von Eckardstein S, et al. World Health Organization reference values for human semen characteristics. *Hum Reprod Update.* 2010;16:231-245.
48. Deruyver Y, Vanderschueren D, Van der Aa F. Outcome of microdissection TESE compared with conventional TESE in non-obstructive azoospermia: a systematic review. *Andrology.* 2014;2:20-24.
49. Schrader M, Muller M, Sofikitis N, Straub B, Krause H, Miller K. "Onco-tese": testicular sperm extraction in azoospermic cancer patients before chemotherapy-new guidelines? *Urology.* 2003;61:421-425.
50. Ginsberg JP, Carlson CA, Lin K, et al. An experimental protocol for fertility preservation in prepubertal boys recently diagnosed with cancer: a report of acceptability and safety. *Hum Reprod.* 2010;25:37-41.
51. Ginsberg JP, Li Y, Carlson CA, et al. Testicular tissue cryopreservation in prepubertal male children: an analysis of parental decision-making. *Pediatr Blood Cancer.* 2014;61:1673-1678.
52. Wyns C, Curaba M, Petit S, et al. Management of fertility preservation in prepubertal patients: 5 years' experience at the Catholic University of Louvain. *Hum Reprod.* 2011;26:737-747.
53. Patel RP, Kolon TF, Huff DS, et al. Testicular microlithiasis and antisperm antibodies following testicular biopsy in boys with cryptorchidism. *J Urol.* 2005;174:2008-2010.
54. Gassei K, Orwig K. Experimental methods to preserve male fertility and treat male factor infertility. *Fertil Steril.* 2016;105:256-266.
55. Johnson EK, Finlayson C, Rowell EE, et al. Fertility preservation for pediatric patients: current state and future possibilities. *J Urol.* 2017;198:186-194.
56. Letourneau JM, Ebbel EE, Katz PP, et al. Pretreatment fertility counseling and fertility preservation improve quality of life in reproductive age women with cancer. *Cancer.* 2012;118:1710-1717.
57. Gupta AA, Donen RM, Sung L, et al. Testicular biopsy for fertility preservation in prepubertal boys with cancer: identifying preferences for procedure and reactions to disclosure practices. *J Urol.* 2016;196:219-224.
58. Alliance for Fertility Preservation. State legislation. http://www.allianceforfertilitypreservation.org/advocacy/state-legislation. Accessed November 11, 2017.