CLINICAL REPORT Guidance for the Clinician in Rendering Pediatric Care

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Fertility Preservation for Pediatric and Adolescent Patients With Cancer: Medical and Ethical Considerations

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Many cancers presenting in children and adolescents are curable with surgery, chemotherapy, and/or radiotherapy. Potential adverse consequences of treatment include sterility, infertility, or subfertility as a result of gonad removal, damage to germ cells as a result of adjuvant therapy, or damage to the pituitary and hypothalamus or uterus as a result of irradiation. In recent years, treatment of solid tumors and hematologic malignancies has been modified in an attempt to reduce damage to the gonadal axis. Simultaneously, advances in assisted reproductive technology have led to new possibilities for the prevention and treatment of infertility. This clinical report reviews the medical aspects and ethical considerations that arise when considering fertility preservation in pediatric and adolescent patients with cancer.

INTRODUCTION

Childhood cancer affects 1 of every 285 children younger than 20 years in the United States. Because of advances in treatment, survival has steadily increased since the 1970s. With increasing survival rates, there are currently more than 375 000 survivors of childhood cancer in the United States, with 70% of them being 20 years or older.[1,2] Improvements in prognosis and survival have been observed for many childhood cancers, including hematologic malignancies, Wilms tumor, malignant bone tumors, and rhabdomyosarcomas. The relative 5-year survival rate for all childhood cancers combined is 83.8%.[2]

With the improved survival rate of children affected by childhood cancer has come a growing population of adult survivors of childhood cancer who are or will be interested in having children. Past and contemporary treatments for childhood cancer, including chemotherapy, radiotherapy, and hematopoietic stem cell transplant, can affect future fertility. In the current era, many children and adolescents who present with a new cancer diagnosis can benefit from fertility-preserving modalities initiated

abstract

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The guidance in this report does not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

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before cancer treatment. Individuals whose previous treatment of childhood cancer led to infertility or sterility can often benefit from fertility treatment options such as egg and sperm donation and gestational surrogacy.

Although not specifically addressed in this report, the same strategies of fertility preservation apply to children facing gonadotoxic therapies for treatment of nonmalignant diseases such as juvenile idiopathic arthritis and Fanconi anemia. Infertility resulting from the treatment of differences of sexual development and as a result of hormonal or surgical gender-affirming therapies for transgender individuals are beyond the scope of this document.

Although this document focuses on adolescents and young adults under the age of 18 years, many individuals who received a cancer diagnosis in childhood continue to be seen by their pediatric providers well into adulthood. As such, these guidelines are generalizable beyond the age of majority and apply to decision-making for adult survivors of childhood cancers as well. Complex ethical considerations arise when counseling families confronting a cancer diagnosis regarding fertility preservation options. The difficulty of such decision-making is often compounded by the frequently limited time available to make decisions that can affect fertility. The differences between male and female reproductive physiology affect the range of options available to boys and girls. Options in adolescents who have undergone puberty are broader than those in prepubertal children. The ideal time to consider fertility preservation is before the initiation of therapies that may decrease fertility or cause sterility, but this sometimes is not possible.

It is important for physicians who care for children who develop cancer or other diseases requiring treatment with gonadotoxic therapies to understand the potential deleterious effects of the various treatments on male and female fertility and to be familiar with the American Society of Clinical Oncology (ASCO) guidelines for fertility preservation in children. Recognizing the risks associated with both radiation and chemotherapy, the ASCO recommends that oncologists (1) use established methods of fertility preservation (semen cryopreservation and oocyte cryopreservation) for postpubertal minor children, with patient assent as appropriate, and parent or guardian consent; (2) present information on additional methods that are available for children but are still investigational; and (3) refer for experimental protocols when available.[3] Establishing relationships with centers and physicians who have expertise in counseling and treating children who may benefit from fertility preservation will help oncologists better streamline care for their patients who are interested in fertility preservation. Oncologists can refer families for consultation to discuss both the effects of therapy and potential fertility preservation options in a timely manner, as long as any delay will not negatively affect the success of their treatment. In so doing, they will prevent missed opportunities for information and interventions related to fertility care.

Recognizing that older adolescents and even young adults may develop cancers that fall under the umbrella of childhood malignancies, this clinical report will include options that may be more appropriate for the patient who is older than 18 years but is still being cared for in a children's hospital.

BACKGROUND

Infertility is defined as the inability to achieve or sustain a successful pregnancy after 12 months or more of regular unprotected intercourse. Earlier evaluation and treatment may be justified on the basis of medical history, such as anovulation or erectile dysfunction. For women 35 years and older, a fertility evaluation is recommended after 6 months of unsuccessful attempts at conception.[4] Although fertility declines with age for both men and women, this decline is much more profound in women. At age 40, half of women will have trouble conceiving. If in vitro fertilization (IVF) is required, the chance of pregnancy per cycle is only 13.9% in women at age 40 and under and 4% in women older than 42 years.[5] For men at age 45, the chance of achieving a pregnancy is much higher, and for these older men, the age of their female partner is the most significant determinant of outcome.[6] The risk of infertility after cancer treatment depends on the type of malignancy and its specific treatment as well as the age of the individual both at the time of diagnosis and at the time that they wish to initiate a pregnancy.[7] In men, treatments can lead to a complete absence of spermatogenesis, a decreased sperm count, or sexual dysfunction. In women, there can be a complete depletion of viable egg production or diminished ovarian reserve, leading to subfertility and a shortened fertile window. A hysterectomy or insult to the uterus may lead to the inability to gestate a pregnancy.

NORMAL PHYSIOLOGY AND FERTILITY POTENTIAL

Differences in the male and female reproductive systems influence available options for fertility after cancer treatment.[8,9] In general, there is a lack of proven options for preservation of fertility in prepubertal boys and girls. The process of spermatogenesis begins in the prepubertal boy, but the production of mature sperm and

steroidogenesis are functions of the adult testes.[10] Spermarche (the release of spermatozoa) is an early- to midpubertal event that precedes the ability to produce an ejaculate and is associated with age-appropriate gonadotropin production.[11,12] There is a large variation in the stage of maturity among 13- to 18-year-old males with respect to sperm production. Once sperm are present, sperm quality in young boys, as determined by a semen analysis, does not seem to be affected by patient age. At this point, sperm can be collected via masturbation, electrostimulation, or surgical sperm extraction, and sperm can then be cryopreserved for future use. It is important to note that not all pediatric centers have electroejaculation equipment available, and surgical extraction requires the expertise of a urologist experienced in this technique. Many boys will, therefore, require referral to a reproductive urologist for these services.[13,14]

In girls, oocyte production peaks in the fetus during midgestation, at which time approximately 6 to 7 million oogonia are present within the ovary. This number decreases to 2 million at birth and to approximately 300 000 at puberty.[15,16] Once menarche has been initiated, mature oocytes develop, and monthly ovulation occurs. At this point, fertility treatments can stimulate multiple eggs, which can be retrieved from the ovary and cryopreserved for later use.

RISK OF INFERTILITY AFTER TREATMENT

Most children treated for cancer can expect to be cured, although the specific chance of cure depends on risk factors at the time of diagnosis, including cancer type, stage, and grade. Although permanent infertility or sterility may occur after cancer treatment, individuals may experience temporary but reversible infertility, a shortened reproductive window, or no compromise in fertility. Many survivors of childhood cancer with intact fertility worry about the potential effects of previous cancer treatment on the health of their offspring.[17] Reassuringly, decades of cumulative experience have shown that naturally conceived biological children of survivors have no increased incidence of congenital malformations,[18–22] genetic or chromosomal anomalies,[23–25] or cancer compared with sibling controls and general population data.[26–33]

Risk of Infertility in the Male Patient After Cancer Treatment

Male fertility can be affected by impairment of spermatogenesis as a result of gonadotoxic chemotherapy, gonadotropin deficiency from central nervous system–directed therapy, or functional abnormalities of genitourinary organs caused by spinal or pelvic surgery and/or radiotherapy. Deleterious effects on testicular function have been observed with alkylating agents, such as cyclophosphamide, as evidenced by increased follicle-stimulating and luteinizing hormone concentrations, indicating decreasing gonadal function.[34–36]

In a large cohort study, the St Jude Lifetime Cohort Study, testicular function was evaluated by using a semen analysis. The investigators performed a semen analysis on 214 adult male survivors of childhood cancer, all of whom had received alkylating agents without radiotherapy. Azoospermia was noted in 25%, oligospermia was noted in 28%, and normospermia was noted in 48%. Importantly, there was no identified threshold dose below which azoospermia did not occur or one above which azoospermia was uniformly present.[37]

Several large studies, including the Childhood Cancer Survivor Study (CCSS),[38,39] have evaluated the fertility outcome of survivors of childhood cancer. The most recent cohort study included almost 11 000 survivors not exposed to gonadal or cranial radiotherapy and more than 3900 sibling controls. On the basis of self-reported data, it was found that male survivors had a decreased likelihood of fathering a pregnancy compared with a sibling control group.[40] This finding confirmed results from an earlier CCSS study showing that among male patients, risk factors for impaired fertility included increasing alkylating-agent exposures and higher testicular radiation doses (Tables 1 and 2). These studies are important in counseling because although increasing chemotherapy and radiation doses are associated with a higher chance of infertility, there is no dose so low as to guarantee the maintenance of fertility and no dose so high that infertility is certain to occur.

Risk of Infertility in the Female Patient After Cancer Treatment

Chemotherapy and tradiotherapy can destroy ovarian follicles and

TABLE 1 Alkylating Agents With Infertility Risk

Alkylating Agents
Classic alkylating agents
Busulfan
Carmustine (BCNU)
Chlorambucil
Cyclophosphamide
Ifosfamide
Lomustine (CCNU)
Mechlorethamine
Melphalan
Procarbazine
Thiotepa
Heavy metals
Cisplatinum
Carboplatinum
Nonclassical alkylators
Dacarbazine (DTIC)
Temozolomide

Adapted from Children's Oncology Group. *Long-Term Follow-Up Guidelines for Survivors of Childhood, Adolescent, and Young Adult Cancers. Version 5.0.* Monrovia, CA: Children's Oncology Group; 2018:12–14. Available at: http://www.survivorshipguidelines.org/pdf/2018/COG_LTFU_Guidelines_v5.pdf. Accessed April 26, 2019.

TABLE 2 Childhood Cancer Therapy Affecting Reproductive Tissues

	Reproductive Effect	Predisposing Therapy	Modifying Factors
Sex			
Both	Altered pubertal timing (precocious, early, rapid tempo), delayed puberty, gonadotropin insufficiency or deficiency	Hypothalamic-pituitary radiation	Altered pubertal timing more common after low-dose radiation at 18–24 Gy, gonadotropin insufficiency more common after radiation at more than 30 Gy
Female	Acute ovarian failure (ovarian failure within 5 y of diagnosis), premature menopause (cessation of menses before age 40 y)	Alkylating-agent chemotherapy, radiation affecting the female reproductive system (whole abdomen, pelvis, lumbosacral spine, total body), oophorectomy	Older age at treatment due at higher risk
	Uterine vascular insufficiency, uterine growth impairment	Radiation affecting the uterus (whole abdomen, pelvis, lumbosacral spine, total body)	History of Wilms tumor and associated Müllerian anomalies
	Vaginal fibrosis or stenosis	Radiation affecting the vagina	History of hypogonadism (estrogen insufficiency), history of chronic graft-versus-host disease
	Sexual dysfunction, dyspareunia	Pelvic surgery, hysterectomy, radiation affecting the uterus or vagina	History of hypogonadism (estrogen insufficiency)
	Spontaneous abortion, neonatal death, premature labor, neonate with low birth wt, fetal malposition	Radiation affecting the uterus (whole abdomen, pelvis, lumbosacral spine, total body)	History of Wilms tumor and associated Müllerian anomalies
Male	Azoospermia oligospermia	Alkylating-agent chemotherapy, radiation affecting the male reproductive system (pelvic, testicular, total body), orchiectomy (bilateral)	Prepubertal status at treatment does not reduce risk
	Retrograde ejaculation, anejaculation erectile dysfunction	Pelvic surgery (retroperitoneal node or tumor dissection, cystectomy, radical prostatectomy), radiation to pelvis, bladder, or spine	History of hypogonadism (androgen insufficiency)

See www.survivorshipguidelines.org for health risks to other organs and tissues resulting from treatment of childhood cancer. Adapted, with permission from Elsevier, from Hudson MM. Survivors of childhood cancer: coming of age. *Hematol Oncol Clin North Am.* 2008;22(2):218.

predispose female patients to diminished ovarian reserve and premature ovarian failure. Premature ovarian failure is defined as premature menopause occurring before age 40. This differs from diminished ovarian reserve, which can lead to increased difficulty in achieving a pregnancy or to a shortened reproductive window despite regular menstrual periods. The deleterious effects of chemotherapy are dependent on the age of the patient at the time of therapy, the specific agents used, and cumulative dosing.[41] Oocytes do not regenerate after birth, as opposed to spermatogenesis, which continues to occur from progenitor stem cells throughout a man's life. Premature ovarian failure is rare in survivors of childhood cancer and was found to have an incidence of 6% to 9% in CCSS cohorts.[42] Many women who do not have overt ovarian failure will have diminished ovarian reserve.[43] Several studies have used anti-Müllerian hormone (AMH) concentrations to estimate ovarian reserve.[44,45] Survivors of childhood cancer often have lower AMH concentrations compared with a control group.[46,47] Low AMH concentrations can predispose to diminished ovarian reserve and, therefore, a higher risk of infertility as well as earlier menopause. When evaluated by treatment exposure (alkylators only, alkylators and subdiaphragmatic radiation, or high-dose alkylating therapy), all survivor groups had diminished ovarian surface area and AMH concentrations. Ovarian reserve was worse when survivors received a high dose versus a conventional dose of alkylating therapy.

Radiation has an effect on both the brain and the end organs. When the brain is the target of irradiation, infertility can present as hypothalamic amenorrhea. High-dose cranial radiotherapy (35–40 Gy) can cause infertility via hypogonadism through its effects on the hypothalamic-pituitary axis. Such infertility can be treated medically with stimulation of the ovaries or testes with gonadotropins to induce the maturation and release of gametes. Radiation can affect the uterus and vagina, and women undergoing radiation to the uterus are less likely to both conceive a pregnancy and carry it to term.[48] Direct pelvic radiotherapy, abdominal or spinal radiation, or scatter radiation can all affect the ovaries. The oocyte median lethal dose for radiotherapy is less than 2 Gy.[49]

Several studies have been focused on infertility and achievement of pregnancy in female survivors of cancer. One CCSS cohort study found that the risk of nonsurgical premature menopause was increased for survivors of childhood cancer.[42] Survivors also had an increased risk of clinical infertility when compared with sibling

controls. This risk was most pronounced in the early reproductive years (≤24 years), when fertility is high in a general population. Increasing doses of uterine radiation and alkylators were most strongly associated with infertility. Promisingly, almost two-thirds of survivors with clinical infertility reported a pregnancy during the study period, which included both those achieving pregnancy spontaneously and those who underwent fertility treatment.[50] Another CCSS cohort study analyzed only survivors who had not received gonadal or cranial radiotherapy to evaluate the effect of chemotherapeutic agents on pregnancy. Just as with male survivors, female survivors had a decreased likelihood of pregnancy and live birth compared with sibling controls. If a pregnancy was not achieved by age 30, the likelihood of ever becoming pregnant by age 45 was further reduced compared with siblings. As with previous studies, the most deleterious chemotherapeutic agents were the alkylating agents, including lomustine and cyclophosphamide.[40]

OPTIONS FOR FERTILITY PRESERVATION

The options, burdens, and costs of fertility preservation differ for boys and girls. The availability of options also differs depending on whether the child facing cancer treatment is prepubertal or postpubertal and on the urgency with which treatment must be initiated. Some treatments are well established and have known efficacy and outcomes data, and others are still experimental. It is important to differentiate between clinically accepted and experimental treatments when counseling patients and families regarding their fertility-preserving options.

PRESERVATION OF FERTILITY BEFORE TREATMENT IN THE PREPUBERTAL CHILD

Fertility preservation in the prepubertal child is challenging. The majority of proposed treatment modalities are thus far experimental in nature and without proven efficacy. The one exception is gonadal shielding or moving the gonads out of the radiation field.[51] Familiarity with these options and the data surrounding them can assist physicians in treating and counseling their patients with cancer. Furthermore, patients who wish to undergo prepubertal fertility preservation attempts may be best served under an institutional review board (IRB)–approved clinical trial so that they can be carefully monitored and their experience used to determine if such therapies should continue to be offered in the future.

Boys

Before puberty, methods available for gonadal and gamete preservation in the male patient are primarily theoretical at the present time, with the exception of shielding the testes or moving them out of the radiation field.[52,53] Most methods involve hormonal and other manipulations to protect the testes from injury during cancer treatment or involve preserving a testicular tissue sample. Primordial sperm cells are susceptible to toxicity at all stages of life. Gonad shielding can be used during radiotherapy but is only possible with selected radiation fields and anatomy and may increase the risk of harboring malignant cells.[3] The gonad(s) can also be temporarily relocated outside of the radiation field to either the thigh or the anterior abdominal wall.[54,55]

To date, no effective pharmacologic intervention has been identified. Gonadal protection through hormone manipulation has been evaluated only in small studies in patients with cancer and is uniformly ineffective in either preserving fertility or speeding the recovery of spermatogenesis.[3] Animal studies suggest that testicular tissue cryopreservation, autotransplantation, xenotransplantation, and in vitro maturation may be successful methods of fertility preservation, but most have yet to be tested in humans.[56] Human spermatocytes have been matured in vitro to mature spermatids, resulting in at least 1 pregnancy.[57] Testicular tissue cryopreservation has been reported, and ongoing clinical trials are being conducted to address prepubertal fertility preservation in boys.[58,59] Oncologists can help their male patients and their families by sharing with them information and options regarding clinical trials to address prepubertal fertility preservation. Once testicular tissue has been cryopreserved, future options for its use may include in vitro maturation or germ cell transplant, which at this time are theoretical in nature.

Girls

Similar to prepubertal boys, most fertility preservation modalities in prepubertal girls are experimental in nature and are without adequate long-term outcomes data. The exception is gonadal shielding and oophoropexy. Shielding of the ovaries during radiotherapy and oophoropexy to remove the ovaries from the radiation field are strategies to preserve ovarian function during treatment, although radiation scatter is a concern despite best efforts to avoid radiation exposure.[60–62] Although ovarian transposition is relatively effective for preserving the endocrine function of the ovary (in 60% of cases), only approximately 15% of patients treated with transposition and wishing to become pregnant ever achieve this goal.[60] Of note, the benefit of gonadal shielding is less effective if adjuvant chemotherapy with gonadotoxic agents is required as part of the treatment regimen.

There are also potential means for preserving ovarian function in selected cases of reproductive tract malignancy, including more conservative surgery for certain early-stage tumors and choosing chemotherapeutic agents that have less gonadal toxicity.[60,63,64]

In prepubescent girls, the ovaries cannot be stimulated to produce mature eggs. Ovarian tissue cryopreservation has been proposed as a method to preserve fertility in this cohort of girls. In contrast to oocyte cryopreservation, ovarian tissue cryopreservation (via removal of a portion of the ovary or unilateral oophorectomy) is a process in which normal, functioning ovarian tissue is excised from the ovary and cryogenically stored.[65–70] Currently, this technique is only available in certain parts of the United States as an open clinical trial to assess its efficacy and safety as a potential option for preservation of fertility in prepubertal girls.[71,72] Within this context, it is the only method that can be offered to prepubertal girls.[73] This technique has been performed in children as young as 2.7 years of age, and the chance of later restoring fertility should theoretically be higher because the ovarian cortex contains more primordial and primary follicles in younger children.[73] Ideally, the stored ovarian tissue is thawed and autotransplanted into the donor once her treatment has been completed.[74] There are no data yet available regarding whether cryopreservation of ovarian tissue in prepubertal girls can lead to pregnancy and delivery. Given the potentially limited viability of the autotransplanted tissue, this procedure is more likely to restore reproductive endocrine function rather than result in preserving fertility, unless the oocytes are retrieved relatively soon after the transplant. Studies using flow cytometric evaluation have confirmed the presence of contaminating leukemia cells in histologically normal pretreatment ovarian tissue specimens removed from patients with leukemia and lymphoma before initiation of treatment, leading to the theoretical concern for reseeding the body with tumor cells after the autotransplant.[75,76] In adults, more than 70 live births have been reported in women who cryopreserved ovarian tissue, but only when the tissue was harvested postpubertally.[77–82] A potential confounder in the various case series in which live births were reported is that in the majority of cases, some native ovarian tissue was present in addition to the autotransplanted ovarian tissue. It is possible that pregnancies occurred from oocytes obtained from the native ovarian tissue and not from the transplanted material.[83]

Until recently, all of the reports of successful births after autografts of cryopreserved ovarian tissue in the pediatric population were obtained from adolescents who had already begun the pubertal transition. There has now been at least 1 published report of a live birth after an autograft of cryopreserved ovarian tissue in a prepubertal girl, who was 9 years old at the time that her ovarian tissue was cryopreserved.[84] Before this, the youngest age at the time of ovarian tissue cryopreservation was 14 years, in a girl preparing to undergo a myeloablative conditioning regimen as part of a hematopoietic stem cell transplant performed for homozygous sickle cell anemia. Although she had not yet achieved menarche, there was evidence that she had already started the pubertal transition on the basis of existence of breast development.[85] Given the unknown efficacy of this technique, ovarian tissue cryopreservation in prepubertal girls is best performed under an IRB protocol.

PRESERVATION OF FERTILITY BEFORE TREATMENT IN THE POSTPUBERTAL ADOLESCENT

Once a male adolescent is able to produce mature sperm or a female adolescent is able to be stimulated to provide mature oocytes, fertility preservation options become more viable. The options for germ cell preservation before treatment differ depending on sex.

Male Adolescents

Sperm cryopreservation after masturbation is the most established and effective method of fertility preservation in male adolescents.[71] Whenever possible, sperm should be collected before initiation of cancer therapy to prevent the risk that sperm DNA integrity or sample quality will be compromised. Sperm can be collected at infertility centers or andrology laboratories and stored either at these sites or at long-term storage facilities. Patients may be shy or embarrassed at the prospect of masturbation, such that a discussion of the available options is best conducted with the patient and his legal guardian(s) in a comfortable and accepting manner. It may be helpful to provide a space for the patient to speak privately with a medical team member in the absence of the parent or guardian to allow the adolescent to ask questions and address concerns. Physicians may be instrumental in guiding parents regarding approaches to effectively discuss sperm cryopreservation with their adolescent sons.[86] One study suggested that adolescent boys may be more successful at masturbation if a parent does not accompany them to the appointment.[87] Underlying sperm quality may be poor in certain cancer types, including testicular cancer, leukemia, and Hodgkin's disease.[88,89] Nevertheless, recent progress in andrology laboratories and with assisted reproductive technology (ART) allows for successful freezing and future use of even a limited

number of sperm and even when the sperm quality is diminished.[90]

Alternative methods of obtaining sperm besides masturbation include testicular aspiration or extraction, electroejaculation under sedation or anesthesia,[91] or retrieval from a postmasturbation urine sample.[87] Although fresh sperm samples may result in higher success rates than frozen sperm, the success rate depends more on the sperm parameters at the time of production than on whether the sample was used fresh or was previously cryopreserved.[92,93] With fair-quality frozen sperm samples, IVF is often recommended to achieve pregnancy rather than intrauterine insemination because cycle success rates are much higher and sperm are a limited resource. In cases in which only a few sperm are present, fertilization and pregnancy can be achieved by performing IVF with intracytoplasmic sperm injection (ICSI).

Female Adolescents

Although postpubertal female adolescents historically had few available options, this has changed over the past decade with improvements in oocyte cryopreservation. Oocyte cryopreservation remains generally more invasive and expensive than sperm harvesting. In October 2012, the American Society for Reproductive Medicine released a statement describing oocyte cryopreservation as no longer experimental and recommending that it be offered to adult patients facing the risk of infertility resulting from chemotherapy and other gonadotoxic therapies.[94] Embryology laboratories are increasingly able to cryopreserve, thaw, and fertilize mature oocytes, with success rates approaching or equaling those achieved with more traditional embryo freezing.[94] This opens up a viable option for the postmenarcheal pediatric patient with cancer.[95,96] Successful pregnancy rates by using previously cryopreserved oocytes have been reported to be as high as 50% in adult women cryopreserving their oocytes but would be expected to be even better in young women and adolescents.[97] Such rates have been obtained at fertility centers that are experienced with egg freezing, and patients should be encouraged to freeze oocytes at centers with ample experience using this technology. The number of infants born from frozen oocytes is increasing. Information on the health outcomes of children born via this specific technique for fertility preservation is limited but has overall been reassuring. No increases in chromosomal abnormalities, birth defects, or developmental deficits have been noted in the children born from cryopreserved oocytes as compared with other standard ART procedures, such as IVF, and with natural conception[98–101]; however, these data are not from patients who cryopreserved their oocytes after a cancer diagnosis. To date, it is not known whether success rates in this situation will mirror those achieved after oocyte cryopreservation for other indications. Nevertheless, given the reassuring outcomes data for egg freezing in other contexts and the lack of other options for many women facing gonadotoxic therapies, the American Society for Reproductive Medicine and the American College of Obstetricians and Gynecologists support the use of oocyte cryopreservation for women at risk for losing ovarian reserve because of gonadotoxic exposures.[102] This technique requires controlled ovarian hyperstimulation with approximately 10 days of subcutaneous gonadotropin hormone injections. Eggs are then retrieved from the ovaries with transvaginal ultrasonography-guided needle aspiration performed under intravenous sedation. As mentioned previously, although medically viable, this technique has limitations in the adolescent age group because of the invasive nature of the process. Although oocyte cryopreservation is a medically viable option beginning around the time of menarche, it is less clear whether it should be routinely offered to young adolescents or to any minor. The process of oocyte cryopreservation requires approximately 10 days of monitoring with transvaginal ultrasonography and blood tests, followed by a transvaginal oocyte retrieval performed under anesthesia. In some clinical situations, a delay of a week or more before initiating cancer treatment may not be possible or may compromise care such that oocyte cryopreservation may not be a viable option. For many adolescents and their parents or guardians, the invasive nature of the ovarian stimulation process and retrieval may prevent its acceptance on psychological and emotional grounds.

Women with hormonally sensitive tumors who are interested in oocyte or embryo cryopreservation present specific challenges because standard protocols for ovarian stimulation are associated with significant (albeit temporary) elevations in estradiol concentrations. Such elevations may theoretically increase the risk of tumor progression and spread.[103] There has been a growing experience with the use of selective estrogen receptor modulators and aromatase inhibitors during the stimulation portion of the cycle. Use of these agents has been shown to significantly reduce peak estradiol levels during ovarian stimulation to those more typical of a spontaneous ovulation during a normal menstrual period, thus theoretically decreasing the risk of stimulating hormonally sensitive tumors. Fortunately, this blunting of the hormones does not have a negative effect on egg quality or cycle outcome. The lower estradiol concentrations in cycles using selective estrogen receptor modulators and aromatase inhibitors do not appear to decrease the chance

of achieving a pregnancy when the resultant embryos are ultimately transferred to the uterus.[104,105]

Cryopreservation of embryos, in which oocytes are fertilized with sperm from the woman's male partner or with anonymous donor sperm, was historically the only option available to postpubertal girls and young women wishing to preserve their fertility. As compared with oocyte cryopreservation, embryo cryopreservation is more socially, emotionally, and ethically complex because the patient needs the maturity to fully comprehend all aspects of the procedure, including the fact that the eggs will be fertilized with (usually anonymous) donor sperm.[67] Given the success rate with oocyte cryopreservation, there is little need to consider fertilizing the eggs before cryopreserving them, and embryo cryopreservation should only be used in rare circumstances, for example, when an older adolescent is married or in a long-term committed relationship. Even then, cryopreserving oocytes opens up more future options than cryopreserving embryos and should be encouraged when available and when the patient is of an appropriate age and maturity level to undergo an ovarian stimulation procedure.

For women who have previously undergone pelvic irradiation, there may be scarring or other postradiation effects to the uterus and vagina that preclude conception or the ability to maintain a pregnancy. For girls who will be receiving pelvic irradiation and their families, discussion of the future use of a gestational surrogate may be warranted. If the ovaries remain functional after irradiation, it will be possible to retrieve eggs from them, fertilize them through IVF, and transfer them into a gestational carrier. When premature ovarian failure has occurred, women with uterine or vaginal compromise who wish to consider parenting options outside of adoption will require both donation from a known or anonymous egg donor and the services of a gestational carrier. There are significant costs associated with this mode of reproduction. Also, gestational surrogacy laws are complex, differ among states, and evolve over time.

There has been speculation that concomitant treatment with gonadotropin-releasing hormone (GnRH) analogs may prevent ovarian failure induced by cancer therapy by protecting against chemotherapy-induced follicle depletion. The studies looking at this option to date were performed on adult women with breast cancer, and it is not clear whether these data are applicable to children. In adults, most studies evaluating GnRH analogs to prevent ovarian failure have not demonstrated benefits,[106–108] although 1 recent randomized trial revealed a significant reduction in ovarian failure and an increased fertility rate in women receiving GnRH analogs.[109] These findings cannot be applied to prepubertal girls, in whom the hypothalamic-pituitary-ovarian axis is still quiescent.[71] The 2018 ASCO guidelines acknowledge that there is conflicting evidence regarding the use of GnRH analogs to protect fertility but suggest that in situations in which proven fertility preservation methods are not feasible, GnRH analogs may be offered to patients, with the hope of reducing chemotherapy-induced ovarian insufficiency.[3]

COSTS OF FERTILITY PRESERVATION

The costs of fertility preservation are often not covered by insurance,[110] especially given that insurance usually does not cover experimental therapies, thus compounding the psychological distress with the economic impact of infertility.[111,112] Some states have comprehensive fertility coverage because of mandates on insurance, and some have recently begun mandating coverage of fertility preservation.[113,114] The later use of stored gametes may be covered under such fertility mandates.[115] Legislative efforts are underway in a number of states to address this issue.[116] Because the cost burden on patients or families can be expected to change over time and by geographic area, good counseling will require familiarity with current regional data.[117] Some patients may benefit from fertility preservation under experimental protocols, and these should be considered when applicable and after appropriate counseling has been provided.

Sperm cryopreservation is a technique that has been used for many years and has associated benefits and a record of success that supports its widespread use in the postadolescent male patient. The cost of sperm cryopreservation after masturbation can total hundreds of dollars a year, with additional costs incurred if alternative methods, such as surgical sperm extraction, are needed to obtain sperm or for prolonged storage.[3] When ready to be used for reproduction, IVF and often ICSI may be needed to achieve pregnancy, especially given the often-limited quantities of sperm available. The relevant costs of IVF are discussed later in this section.

In postmenarcheal female adolescents, controlled ovarian hyperstimulation for the purpose of retrieving and cryopreserving oocytes is often not covered by insurance. The various components of such cycles include (1) stimulating the ovaries with daily subcutaneous injections over the course of 8 to 21 days and monitoring of the ovarian response with approximately 5 blood tests and ultrasonographic examinations over the course of the stimulation; (2) the cost of gonadotropins to stimulate the ovaries, medications to prevent early

ovulation, and medications to blunt the estrogen response in cases of hormonally sensitive malignancies; (3) egg retrieval under anesthesia; (4) embryology and laboratory fees; and (5) cryopreservation of the oocytes. A typical oocyte cryopreservation cycle can cost between $7000 and $14 000.[118–121] Medications per egg retrieval cycle can cost between $2000 and $7000, although currently, some pharmacies and pharmaceutical companies provide these medications at a discount or at no cost to patients with a cancer diagnosis. Storage fees for cryopreserved oocytes are approximately $350 to $600 per year.[3] When cryopreserved eggs are ready to be used for reproduction, there are additional costs associated with thawing the eggs and fertilizing them with sperm as well as transferring the embryos back to the uterus.

Women requiring an egg donor because of ovarian failure or diminished ovarian reserve may incur additional costs, particularly if they need to use eggs from an anonymous egg donor, who is reimbursed for her contribution. Women who require a gestational surrogate because of an inability to carry a pregnancy will incur costs of both IVF and gestational surrogacy, which often total in the tens of thousands of dollars.

Experimental fertility preservation options may be covered under a research protocol in some cases such that there may be no or minimal costs to the patient. The therapies themselves can be expensive. Once they are no longer considered experimental, the cost will be borne by the families of children using them in the future to the extent that insurance does not provide coverage.

For prepubertal boys, testicular tissue cryopreservation is a potentially costly option that has not yet proven to result in offspring in humans but has been successful in primates.[122] If successful, the tissue would either need to be retransplanted into the testes or some extratesticular location, and/or sperm would need to be extracted from the tissue after sperm maturation. If sperm were to be extracted, then IVF and ICSI would need to be used in the future to obtain viable embryos.

For prepubertal girls, the costs of ovarian tissue preservation can be separated into 3 parts: (1) the procedure to retrieve the tissue, generally laparoscopy and attendant anesthesia[123]; (2) ovarian tissue pathologic evaluation and freezing; and (3) the annual cost of ovarian tissue storage. Laparoscopic procedures, even in children, often can be performed on an outpatient basis, precluding an inpatient hospitalization cost.[74] The cost of ovarian tissue freezing alone might be similar to that of freezing testicular sperm after testicular dissection (see previous discussion), incurring an annual cost for ovarian tissue storage of several hundred dollars a year or greater. Assuming recovery of the patient after treatment, the costs will include tissue thawing and the procedure for autotransplantation, subsequent medications, and laboratory testing. Ovarian tissue preservation remains experimental and is best performed at a specialized center and under IRB approval. In some cases, enrollment in such studies does not incur a cost to the participants.

Counseling Families Regarding Options for Fertility Preservation

Counseling regarding fertility preservation options is the first step in assisting families in navigating options for fertility preservation. This counseling is best undertaken as early as feasible after a cancer diagnosis is made and before the initiation of any cancer treatment, if possible. For preadolescents, it is appropriate for one or both parents or guardians to be present for such conversations. Adolescents may benefit from the opportunity to speak one on one with their physician and/or child psychologist or reproductive specialty surgeon in the absence of their parents. For adolescent girls who may benefit from oocyte cryopreservation, a frank discussion regarding their experience with tampon use and intercourse should be undertaken because the monitoring that is required before retrieving the oocytes requires multiple transvaginal ultrasonographic examinations. For adolescent boys, a discussion of sexual experience and comfort with masturbation should occur. Recognizing that fertility preservation may create both burdens and opportunities for patients and their families, discussions regarding reproductive potential have, as their goal, the maximization of the child's future options and well-being.

Most often, a child will initially present to the general pediatrician and then be referred to a pediatric hematologist oncologist. Physicians involved in cancer treatment should be familiar with the ASCO guidelines for fertility preservation[3] and be able to provide referral for consultation and treatment to patients and families who wish to seek these out. When possible, a child should be referred to a multidisciplinary team for a comprehensive approach to the evaluation of options for fertility preservation for his or her specific circumstances. This team can provide counseling regarding appropriate treatments, their timing, and their scope. The team may consist of the patient's primary care physician, pediatric hematologist and oncologist, radiation oncologist, reproductive endocrinologist, urologist specializing in male infertility, surgeon (if surgery is part of the treatment), child-life or other integrative health specialist, and mental health professionals. Ethics consultants may be helpful when conflicts arise between medical

professionals and the patient and family.[124] Such a team approach allows families to obtain the information they require to make decisions regarding fertility preservation and allows those who decide to pursue fertility preservation options to do so in an efficient manner and maximizes the chance that fertility preservation options are initiated before starting cancer therapy. For prepubertal children, consultation with and/or referral to a center performing testicular and ovarian cryopreservation under an IRB protocol is appropriate. The type, stage, and severity of the cancer affect the time frame during which decisions surrounding fertility preservation must be made. In some cases, these decisions must be made emergently, whereas in other cases, the window for action is urgent but not emergent. In some circumstances, lifesaving treatment will need to start immediately and fertility preservation options will not be available. Even when fertility preservation is not possible because of the need for treatment or other determinants, counseling regarding the risks to fertility inherent in the various treatment options will allow patients and their families to cope with the effects of cancer treatment.

Counseling Regarding Expected Outcomes After Fertility Preservation

Physicians have an important role in counseling children and their caregivers regarding their future reproductive options when faced with a cancer diagnosis. The option of fertility preservation may be of great comfort for patients and their families and may assist them in managing the emotional trauma of the cancer diagnosis,[60] although the offer may also result in unrealistic expectations.[125] Most younger patients with cancer have historically been left with significant anxieties and insufficient information about reproductive issues.[126] Appropriate counseling of parents and patients (as appropriate for age) in developmentally appropriate language will help patients and their families understand the likelihood that cancer treatment will permanently affect fertility. Reproductive endocrinologists and urologists can be instrumental in explaining the pre- and posttreatment options and may help alleviate these anxieties.[3] The downstream options of adoption, egg and sperm donation, and gestational surrogacy can be discussed as well as the success rates, costs, surgical risks, and experimental nature of specific ART options and the acceptability of the option to decline the intervention.[125,127] As part of this discussion, families and children (as appropriate for age) should be made aware that cancer treatments do not guarantee a loss of reproductive potential and that pregnancy can occur in sexually active postpubertal adolescents and young adults. The complexity and impact of the various fertility preservation options may be overwhelming to children and their families. Whenever possible, the information should be conveyed incrementally over multiple visits. This will allow families the time to internalize the various treatment options and determine the optimal course of action for their particular situation. However, some clinical diagnoses do not allow for the luxury of time between identification of the cancer and implementation of treatment, and fertility preservation decisions must be made urgently.

Dispositional Control of Cryopreserved Reproductive Tissue

The fertility specialist can play an important role in discussing the issue of dispositional control of reproductive tissue in the event of the patient's death or incapacity. Such discussions best occur before the collection of any reproductive tissue. Posthumous use of reproductive tissue is defined as the use of gametes or embryos in an attempt to create offspring after the death of the individual who provided the reproductive tissue. Posthumous reproduction from gametes procured in childhood should not occur if the child does not survive beyond the age of majority. This is further discussed below in the section on ethics. Consent forms should designate that the disposition of reproductive tissue will be delayed until the child reaches the age of majority or discarded if the child does not survive to the age of majority. Once the child becomes an adult, he or she can make changes to the disposition of the reproductive tissue, including provisions for its posthumous use. Legal review of the institutional consent process and associated documentation can be considered to preclude future misunderstanding or a misinterpretation of tissue or specimen disposition or disposal. Because case law has evolved in the area of disposition of previously collected embryos and gametes, which has not always strictly enforced documentation in a consent form, periodic review of the program's written consents by an institutional attorney may be helpful. For this reason, involving an attorney as part of the team can be beneficial to families and medical personnel. Once the child reaches the age of majority, he or she should issue new documentation regarding his or her wishes for future storage of previously collected reproductive material.

It should also be disclosed that success rates are not guaranteed. Even with successful collection and freezing of eggs, sperm, and/or embryos, success rates will never be 100%; some children who go through the process of fertility preservation will not ultimately be successful in using their cryopreserved reproductive tissue. Additionally, there are no guarantees that stored embryos and gametes will be viable when ready for reproductive use or

be free of neoplasia. Also, unexpected catastrophes, both natural and man-made, can lead to unintended damage to or destruction of reproductive tissue.

Barriers to Receiving Counseling

Survey results of adult male and female survivors of cancer of reproductive age and studies evaluating oncology practice patterns for discussing infertility have suggested that a conversation with patients with cancer regarding the potential consequences of their treatment on future fertility was lacking in more than half of cases.[3] Pediatric oncologists admit that, despite their motivation to preserve fertility in their patients and their belief that all pubertal patients with cancer could benefit from a fertility consultation, they do not use the ASCO fertility preservation guidelines[3] and instead refer their patients to fertility specialists only a minority of the time.[128] Oncologists provide many different explanations for not referring patients for fertility preservation, including not recognizing the importance of this issue, assuming that patients cannot afford fertility preservation procedures, feeling emotionally uncomfortable discussing the topic, or choosing not to refer the patient because of a poor prognosis.[73] Additional barriers include beliefs that such discussions will add additional stress to an overwhelmed family or will violate provider or family cultural taboos on issues of sexuality. Even when counseling does occur, family satisfaction with the process is often lacking; in one study, only 30% of parents were satisfied with the fertility preservation counseling they received regarding their children.[129] In a survey study identifying reproductive concerns of adolescent girls with cancer and their parents, the concerns of the respective groups were not congruent. Parents incorrectly expected their daughters to be satisfied with only survivorship and less concerned about reproductive potential.[130] In another study in which families were to recall discussions they had regarding fertility expectations after surviving cancer, only about half of parents recalled receiving information on the topic and nearly one-third expected normal fertility.[131]

Patients themselves are generally asking for this information and have identified preservation of fertility as extremely important.[17] Most men taking one survey responded that they believed having experienced cancer increased the value they placed on family closeness and would make them better parents.[132] For men who desire children in the future, lack of timely information is the most common reason for not banking sperm. A survey of adolescent patients with cancer revealed that 81% would want to undergo investigational or research-based procedures to attempt to maintain their fertility.[133] Additional data suggest that the process of fertility preservation, in and of itself, may be therapeutic; for example, young male survivors demonstrated lower distress and enhanced coping with cancer treatment simply from the knowledge that they had stored sperm.[134,135] In addition, the long-term morbidity associated with infertility and interrupted childbearing is not minor and persists well into adulthood.[136] In addition to fertility preservation options, strategies to help survivors of cancer identify and deal with unresolved grief about cancer-related infertility are important health care interventions.

Despite its perceived importance, the process is not easy for patients and families. Making an appointment with the andrology laboratory usually is the responsibility of the patient and family. Chemotherapy induction may need to proceed expeditiously and may not allow the luxury of time for needed consultations and decision-making or may preclude the ability of the patient to provide more than 1 or 2 samples.[87] Facilitating the andrology laboratory visit and delaying the initiation of chemotherapy, if possible, are 2 approaches that might be used in appropriate cases to increase fertility options of survivors of cancer. Some situations are true medical emergencies (eg, respiratory compromise from a mediastinal lymphoma) or are significantly urgent to preclude even the short delay required for an andrology laboratory visit.

Currently available fertility preservation options are not believed to compromise the success of cancer therapy or adversely affect a survivor's health.[3] Other than hereditary genetic syndromes, large registry studies have failed to demonstrate an increased risk of genetic abnormalities,[19,23] congenital malformations,[20–22] or cancers in the children of survivors of cancer.[26–30,32,33] Disclosing this information to patients and families will provide reassurance of the potential value of fertility preservation.[137] For families with hereditary conditions that are risk factors for developing malignancies, the development of preimplantation genetic testing of embryos allows couples to undergo IVF and screen their embryos for the hereditary cancer syndrome for which their offspring is at risk. By electing not to transfer affected embryos, the risk of transmitting cancer genes to their offspring is dramatically reduced. This approach is supported by the American Academy of Pediatrics as well as by the Ethics Committee of the American Society for Reproductive Medicine for couples who wish to avoid having children with high-risk cancers.[138]

One difficulty in counseling either sex regarding risks to future fertility is that there are few absolutes, and the

discussion should be focused on a risk assessment. Some treatments have a high risk of infertility, diminished ovarian reserve, sterility, and/or premature ovarian failure. Other treatments are less likely to lead to the inability to have children. The level of concern over the potential loss of fertility should be addressed, and the spectrum of fertility options that are available to an individual should be presented.

ETHICAL CONSIDERATIONS

Fertility preservation raises several ethical issues, including the dilemma of counseling someone who has not yet reached adulthood, obtaining appropriate consent and/or assent,[125,139] managing disagreements between desires of the patient and his or her family, and later use and disposition of reproductive tissue that was acquired before the age of assent.

A central ethical concern for children facing a cancer diagnosis whose treatment may limit future fertility is that of supporting the right to an open future.[140] This encompasses a set of moral rights children possess that are derived from the autonomy rights of adults. These rights protect children from having important decisions made by others before they have had the ability to make them for themselves. The right to an open future encompasses strategies that may safeguard a child's future fertility.[141]

Of critical concern is the extent to which the minor child should be involved in decisions surrounding his or her care. Guidance on patient participation in decision-making and assent should comply with recommendations in the American Academy of Pediatrics policy statement "Informed Consent in Decision-making in Pediatric Practice."[142]

The patient's family and physicians should work together to help provide an open future for the child. At times, there may be disagreements between a parent and child or between the family and the physicians regarding fertility preservation. Reasons for this include the cultural or religious beliefs of the family or discomfort surrounding discussions of an intimate nature with a child who has not yet or only just recently reached sexual maturity. Parents should be cognizant of their biases and work to maximize options for their children. Although they may not feel completely comfortable with fertility preservation, it is important to consider that the child will become an adult who will make reproductive decisions regarding their fertility.

When possible, after the child has become an adult, he or she should have the broadest possible options from which to choose given the medical circumstances of his or her cancer diagnosis. The opportunity to parent a biologically related child is an important option to attempt to preserve for the child. Recognizing the limits of safety and current technology, medical providers should strive to discuss these options and help provide access to them. Special circumstances might be posed by specific religious beliefs or cultural values that preclude either discussing or allowing ART or that prohibit masturbation.[110] The parent(s) or guardian(s) will most likely be transferring their beliefs to the clinical situation, and these beliefs may or may not represent those of the child at the present time or in the future. Individuals who will later wish to have biologically related children may be adversely affected by decisions that are made for them by their parents or guardians. In some cultures, a person's status in their community may be culturally dependent on their ability to reproduce. It may be helpful, when such options are presented to an adolescent who is mature enough to provide assent, to discuss them without a legal guardian present to help elucidate the adolescent's feelings regarding such decisions. Such discussions should take place regardless of the child's sexual orientation because reproductive considerations remain the same as for any child. When conflicts between patient and family desires arise, involving mental health professionals and/or an ethics consultant to work through the contrasting desires is often helpful and should be considered.

Issues may arise with disposition of gametes (sperm, oocytes, embryos, or gonadal tissue) whether the child lives or dies.[110,143,144] Any procedure performed has as its aim the preservation of a child's reproductive future, and this should be discussed as part of the consent and/or assent process. If the child survives, decisions surrounding disposition of the gametes should be delayed until after the child has reached the age of majority. This stands in contrast to organ donation, in which parents do have control over donation decisions. The contrast between gamete and organ donation stems from the capacity of gametes to propagate the genome of the deceased. Posthumous gamete use in adults is ethically complex. In minors who have not survived to the age of majority, use of cryopreserved gametes is ethically impermissible. It is unethical for parents or legal guardians to arrange for gametes to be fertilized for the purpose of reproduction. The only individual ethically able to consent to the use of their gametes for reproduction is the child who has reached the age of majority. Organs and other tissues are donated for the purpose of saving a life or improving the health of another. Posthumous gamete donation does not serve either of these purposes. These issues are not unique, have precedent in case law, and need to be addressed by any person agreeing to the preservation of tissue or gametes.[144]

Eggs, sperm, and testicular and ovarian tissue obtained from a child who does not survive into adulthood should be discarded. Because a child or an adolescent who lacks capacity cannot give consent to have donated gametes used for procreation and to avoid the risks inherent in the creation of a "commemorative child," parents would not have discretion over the biological material of a child who has died, and the gametes should be destroyed. This is consistent with recommendations made by the American Society for Reproductive Medicine and the European Society of Human Reproduction and Embryology.[145,146]

GUIDANCE FOR COUNSELING OF PARENTS AND PATIENTS ABOUT PRESERVATION OF FERTILITY OPTIONS IN CHILDREN AND ADOLESCENTS WITH CANCER

1. Physicians providing cancer treatment to children should be able to counsel patients and their families regarding the risk of infertility and fertility preservation options. Although there will be cases in which cancer treatment must be initiated emergently and fertility preservation will not be an option, the impact of the treatment on fertility should be discussed.
2. When medically effective fertility preservation options exist, patients and their families should be offered timely referral to centers and providers offering these options. This may include delaying treatment to allow for fertility preservation to occur, as long as the delay does not compromise the success of the cancer therapy.
3. Physicians who provide cancer treatment should be aware that fertility preservation options are limited in prepubertal children and that most treatments in this age group are experimental at the present time.
4. When counseling families regarding fertility preservation, physicians should be clear as to whether the treatments have proven efficacy or are experimental in nature. Experimental therapies should only be undertaken under IRB approval.
5. Evaluation for candidacy for fertility preservation should be guided by an institutional policy. Such policies should be informed by a team of specialists that may include a pediatric oncologist, a specialist in reproductive medicine, a urologist with expertise in male fertility, a radiation oncologist, an ethics consultant, an expert in reproductive law, and a mental health professional.
6. Cryopreservation of sperm and oocytes should be offered whenever possible to postpubertal patients or families of adolescents, dependent on the predicted gonadotoxicity of the prescribed treatment.
7. Given the success that has been achieved with cryopreservation of oocytes, embryo cryopreservation should not be considered in children. Experience with oocyte cryopreservation is variable, and patients should be referred to fertility centers with significant experience and success with this technique.
8. The option of ovarian tissue cryopreservation for female children and adolescents and of testicular tissue in male children and adolescents is still considered experimental and should be offered only in selected institutions in the setting of a research protocol.
9. In considering actions to preserve a child's fertility, parents should consider a child's assent, the details of the procedure involved, and whether such procedures are of proven utility or are experimental in nature.
10. Instructions concerning disposition of stored gametes or gonadal tissue in the event of the patient's death, unavailability, or other contingency should be formally recorded at the center where the gametes or tissue will be stored and should include the patient if possible before collection of the tissue and/or germ cells. There should be another discussion between the patient and the physicians at the center where the reproductive tissue is stored about disposition of gametes after the child reaches the age of majority. Eggs, sperm, and testicular and ovarian tissue obtained from a child who does not survive into adulthood should be discarded by the center preserving the reproductive tissue as per the consents signed at the time of cryopreservation.
11. When conflicts arise between the parent and child regarding fertility preservation, all possible attempts should be made to support an open future for the child while respecting the family's wishes.

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ABBREVIATIONS

AMH: anti-Müllerian hormone
ART: assisted reproductive technology
ASCO: American Society of Clinical Oncology
CCSS: Childhood Cancer Survivor Study
GnRH: gonadotropin-releasing hormone
ICSI: intracytoplasmic sperm injection
IRB: institutional review board
IVF: in vitro fertilization

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