American Academy of Pediatrics
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TECHNICAL REPORT

Preservation of Fertility in Pediatric and Adolescent Patients With Cancer

Mary E. Fallat, MD, John Hutter, MD, the Committee on Bioethics, Section on Hematology/Oncology, and Section on Surgery

ABSTRACT

Many cancers that present in children and adolescents are curable with surgery, chemotherapy, and/or radiation therapy. Potential adverse consequences of treatment include sterility, infertility, or subfertility as a result of either gonad removal or damage to germ cells from adjuvant therapy. In recent years, treatment of solid tumors and hematologic malignancies has been modified in an attempt to reduce damage to the gonads. Simultaneously, advances in assisted reproductive techniques have led to new possibilities for the prevention and treatment of infertility. This technical report reviews the topic of fertility preservation in pediatric and adolescent patients with cancer, including ethical considerations.

www.pediatrics.org/cgi/doi/10.1542/peds.2008-0593

doi:10.1542/peds.2008-0593

Key Words
fertility, infertility, cancer, cancer survivor, late effects, childhood

INTRODUCTION

During the past 40 years, survival rates from many childhood cancers have increased dramatically.[1] Approximately half of childhood cancers are hematologic malignancies (leukemia and lymphoma), and the anticipated long-term survival for children with these disorders is now greater than 75%. Improvements in prognosis and survival have also been observed for many other childhood malignancies, including Wilms' tumor, malignant bone tumors, and rhabdomyosarcomas. The relative 5-year survival rate for all childhood cancers combined is 78%.[2] It has been estimated that approximately 200 000 people who reside in the United States are survivors of childhood cancer.[3]

Past and contemporary treatments for childhood cancer can affect future fertility. For purposes of this discussion, sterility is defined as the inability to conceive a pregnancy naturally in the absence of clinical interventions.[4] Clinical infertility is recognized as the inability to conceive after 1 year or more of unprotected intercourse during the fertile phase of the menstrual cycle.[5,6] The baseline incidence of sterility is estimated at 1% of the general population, and this percentage does not change with age during the window of reproductive potential. Fertility begins to decline when women reach their late 20s and when men reach their late 30s.[4] The prevalence of infertility is estimated at 8% for women aged 19 to 26 years and gradually increases to 18% for women aged 35 to 39 years. This compares with an increase from 18% if the male partner is 35 years old to 28% if the male partner is 40 years old. The risks of infertility after cancer treatment variably affect these numbers depending on the type of malignancy and its specific treatment.[7]

NORMAL PHYSIOLOGY AND POTENTIAL FOR FERTILITY

The differences in the male and female reproductive systems influence available options for fertility after cancer treatment.[2,8] Spermatogenesis begins in the prepubertal male, although spermatogenesis and steroidogenesis are functions of the adult male testes.[9] Meiosis is a relatively early event that is completed by the time of maturation to spermatids. Spermatogenesis depends on the capacity of the totipotential stem cells to undergo self-renewal and provide progeny that mature into viable spermatocytes. Postmeiotic spermatocytes occasionally may be seen in children as young as 4 years. Prepubertal boys have not yet developed gametes. 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.[10,11] There is a large variation in the stage of maturity among 13- to 18-year-old boys with respect to seminal plasma. Once sperm are present, sperm quality does not seem to be affected by patient age. In at least 1 study, sperm concentration, motility, and morphology showed the same pattern in 12 pubertal boys with cancer who were 14 to 17 years of age as in 210 men with malignancies who were older than 20 years.[12,13] Spermaturia is present in 1% to 2% of boys at 11 years of age, 15% to 37% at 12 to 13 years of age, and 24% to 69% at 14 years of age.[14]

It is generally accepted that in females, oocyte production ceases during fetal development, with a finite number of oocytes present at birth.[15] A few oocytes will be released during reproductive life as a consequence of ovulation, and most will be lost as a result of atresia.[16] Although recent animal studies have suggested that primordial germ cells in vitro are capable of forming oogonia and follicle-like structures[17] and that ovarian regeneration may occur from stem cells or arise from stem cells in the bone marrow,[18] these studies are problematic. They have been performed in rodents (interspecies differences can be profound), and evidence that fertility can be modified through these techniques is limited or lacking (even in rodents).[19]

RISK OF INFERTILITY AFTER TREATMENT

Most children treated for cancer now can be expected to be cured and remain fertile,[20] although many contemporary treatment modalities for childhood cancer can affect fertility. Several large studies have evaluated the fertility outcome of childhood cancer survivors. During the 1970s, a multicenter study of 5-year survivors of solid tumor cancers and Hodgkin's disease who were diagnosed before they were 20 years of age demonstrated a 15% incidence of impaired fertility, with problems more prevalent in boys than in girls.[21] Subsequent follow-up studies of childhood, adolescent, and young adult cancer and bone marrow transplant survivors have further defined variables associated with decreased fertility after cancer treatment.[22] These variables include (1) older age and/or developmental maturity of the patient at the time of therapy,[23] (2) the type of therapy,[24] (3) the site of therapy, and (4) gender. For example, the administration of alkylating agents seems to involve more of a risk of infertility in boys compared with the same therapy administered to girls,[21] although the alkylating agents destroy the primordial ovarian follicles in a dose-dependent manner.[25]

The dose of chemotherapy that will render a patient sterile will vary with his or her age and developmental maturity at the time of therapy.[26–28] Older children are more likely to be left infertile. In addition, gonadal toxic effects of chemotherapy during therapy will vary with the type of chemotherapeutic agent, dose, and schedule of administration.[1] Agents that are more likely to pose a risk to gametes include alkylating agents, cytarabine, vinblastine, cisplatin, and procarbazine, among others. Participation in therapeutic clinical trials allows concurrent assessment of efficacy and risk, with the ultimate goal of reconsidering and adjusting regimens so that efficacy is preserved and risks are reduced.

Follow-up studies of sperm production and gonadal function performed on adolescent and young adult male survivors of Hodgkin's disease have shown that both the chemotherapeutic regimen and dose intensity are important variables that affect reproductive potential. Adolescent boys and young men treated for Hodgkin's disease with 6 cycles of chemotherapy, including nitrogen mustard, vincristine, prednisone, and procarbazine, had a greater than 90% risk of infertility, primarily attributable to azoospermia.[29,30] In contrast, azoospermia occurred in only 50% of patients receiving 3 cycles or fewer[29] and in 33% of patients treated with an alternative regimen of adriamycin, bleomycin, vinblastine, and dacarbazine.[1]

The effect of chemotherapy on ovarian function and subsequent recovery is often unknown. In addition to infertility, female survivors of childhood cancer may be at risk of premature ovarian failure or early menopause.[31] Risk factors include institution of therapy after the onset of puberty, administration of alkylating agents such as procarbazine and cyclophosphamide, and the delivery of radiation therapy at doses of 1000 cGy and higher to the region of the ovaries.[25,32] The relative risk of early menopause is also significantly greater for women who have received a combination of alkylating therapy and radiation therapy below the diaphragm, compared with either modality alone.[23,31]

For radiation therapy, variables for infertility risk also include the (1) age and developmental maturity of the patient, (2) dose and fractionation of therapy, and (3) site of radiation therapy. The oocyte median lethal dose for radiation therapy is less than 2 Gy,[33] and sperm production is susceptible to damage at doses of more than 1.2 Gy.[28,34] Testicular Leydig cell function seems to be present at radiation doses up to 20 Gy.[2]

Recognizing the risks associated with both radiation and chemotherapy, the American Society of Clinical Oncology[35] has recommended that oncologists address the possibility of infertility with patients treated during their reproductive years and be prepared to discuss fertility-preservation options or refer patients to reproductive specialists as indicated. However, there is not consensus or direction on when the age of reproductive potential actually occurs or at what age patients should be referred, making it unclear how these recommendations should apply to patients with cancer who are younger than 18 years.

The issues related to considering preservation of fertility in patients younger than 18 years include whether the gonads or gametes have achieved reproductive potential and limitations of the patient and/or partner to understand or consent to necessary procedures. Before considering the unique circumstances of pediatric patients with respect to these issues, it is important to understand what options for fertility preservation are available.

PRESERVATION OF NATIVE GONADAL TISSUE DURING TREATMENT

Males

Before puberty, the only theoretical methods available for gonadal and gamete preservation involve hormonal and other manipulations to protect the testes from injury during cancer treatment. Primordial sperm cells are susceptible to toxicity at all stages of life. Gonad shielding can be used during radiation therapy but is only possible with selected radiation fields and anatomy.[35] The gonad(s) can also be temporarily relocated outside of the radiation field to either the thigh or the anterior abdominal wall.[36,37] In all studies to date, no effective interven-

tion has been identified. Gonadal protection through hormone manipulation has been evaluated only in small studies of patients with cancer and is uniformly ineffective in either preserving fertility or speeding recovery of spermatogenesis.[35] Animal studies suggest that testicular cryopreservation, autotransplantation, xenotransplantation, and in vitro maturation may be successful methods of fertility preservation, but most of these methods have yet to be tested in humans.[2] Human spermatocytes have been matured in vitro to mature spermatids, resulting in at least 1 pregnancy.[38] Testicular-tissue cryopreservation has been reported in 2 boys, with only spermatogonia (ie, cells that are the progenitors of spermatocytes) detected in 1 specimen.[39] The options for this specimen in the future include in vitro maturation or germ-cell transplantation.

Females

Gonad shielding during radiation therapy and oophoropexy to divert the ovaries from the radiation field are potential strategies for preserving ovarian function during treatment.[25,40] Although ovarian transposition is relatively effective at preserving the endocrine function of the ovary (in approximately 60% of cases), only approximately 15% of patients who wish to become pregnant ever achieve this goal.[25] There are also potential means of 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.[41] Germinal and stromal tumors of the ovary are more common in young women and children. Stage Ia dysgerminoma may be managed with unilateral adnexectomy and preservation of the uterus and contralateral adnexa. Early-stage epithelial ovarian cancer (stage Ia), which is less common in children and adolescents, may be managed with unilateral ovariectomy,[25,42] which preserves the chance of natural pregnancy. The overall prognosis for stage I borderline tumors of the ovary is good, and most authors have concluded that conservative treatment increases the risk of recurrence but does not increase the mortality rate.[41,42]

Uterine choriocarcinoma is seen in young people. Tumors with a good prognosis are managed with single-agent chemotherapy by using agents such as actinomycin D or methotrexate, and subsequent fertility rates are reported to be good.[25]

Recently, there has been speculation that concomitant treatment with gonadotropin-releasing hormone analogs may be a promising approach for preventing ovarian failure induced by cancer therapy. The gonadotropin-releasing hormone analog may protect against chemotherapy-induced follicular depletion, thus preserving primordial follicles. Although some studies have been performed in adult patients with cancer, these studies have not yet been extended to children.[43] However, a recent review on this topic in adults concluded that the effectiveness of the intervention is controversial.[44]

FERTILITY PRESERVATION BEFORE TREATMENT

The options for fertility preservation before treatment are different depending on gender. Boys have more available options that are less invasive, less expensive, and more effective and do not require their choosing a partner at the time that they avail themselves of fertility preservation.

Males

Sperm cryopreservation after masturbation is the most established and effective method of fertility preservation in males.[35,45] Sperm should be collected before initiation of cancer therapy because of the risk that sperm DNA integrity or sample quality will be compromised. Underlying sperm quality may be poor for patients with certain cancer types, including testicular cancer, leukemia, and Hodgkin's disease.[46] Nevertheless, recent progress in andrology laboratories and with assisted reproductive techniques allows successful freezing and future use of a very limited amount of sperm, even in cases such as these.[47] Collection of semen through masturbation in adolescents may be compromised by embarrassment and issues of informed consent.[48] Alternative methods of obtaining sperm besides masturbation include testicular aspiration or extraction, electroejaculation under sedation or anesthesia,[49] or from a postmasturbation urine sample.[48] Testicular aspirates do not freeze well and cannot be used as a method of preserving sperm. Published success in creating a viable embryo that results in a living child with any of these methods is limited to case reports.

Females

The collection of mature oocytes requires ovarian stimulation, has been used only in adult patients to date, and may be contraindicated if a cancer is estrogen sensitive.[45,50,51] Because of their large size, water content, and chromosomal architecture, mature female oocytes are extremely fragile. The spindle apparatus of the chromosome is easily damaged by intracellular ice formation during the freezing or thawing process.[52] Therefore, the number of pregnancies resulting in successful deliveries after using cryopreserved oocytes has been small. In addition, because the number of infants born from frozen oocytes is small, information on the health outcomes of children born as a result of this technique versus other techniques of advanced reproductive technologies is lacking.

Ovarian-tissue cryopreservation is a process in which normal, functioning ovarian tissue is excised from the ovary and stored cryogenically.[53–57] Currently, this technique is available only in certain parts of the United States as an experimental protocol until more can be learned about its safety and efficacy.[45] Within this context, it is the only method that can be offered to prepubertal girls.[50] There are a large number of immature oocytes in the ovarian cortex at this age, when the primordial follicles contain prophase I oocytes. This technique has been accomplished in children as young as 2.7 years of age, and the chance of later restoring fertility should be higher, theoretically, because the ovarian cor-

tex contains an increased number of primordial and primary follicles in younger children.[50] Ideally, the stored ovarian tissue is thawed and autotransplanted into the donor once treatment has been completed.[58] However, although the efficiency of ovarian-tissue autografting and/or in vitro maturation has been demonstrated in animals, studies in humans are still in their infancy.[59,60] Recently, successful pregnancies have occurred in cancer survivors after autotransplantation of cryopreserved ovarian tissue.[61,62]

Embryo cryopreservation is an established technique with acceptable pregnancy rates, but its use is limited to females who are either involved in a stable relationship or willing to identify a known or anonymous donor because of the need for sperm.[54] The need for ovarian stimulation theoretically precludes this option for women with estrogen-sensitive tumors, although the use of aromatase inhibitors during stimulation has been proposed as a way of mitigating this concern.[57]

EXPERIMENTAL ANIMAL STUDIES WITH ONCOFERTILITY POTENTIAL

Investigators have developed in vitro three-dimensional follicle-culture systems that mimic the stromal microenvironment of the ovary to produce meiotically competent oocytes that are capable of being fertilized and resulting in live birth of viable murine offspring.[63] Other investigators have shown that bone-marrow transplantation restores oocyte production in wild-type mice sterilized by chemotherapy,[18] although these studies have yet to be duplicated. Daley[64] recently reviewed the prospects of gametogenesis from embryonic stem cells and noted that clinical use of embryonic stem cell–derived gametes seems temporally remote. However, this technology would theoretically eliminate the need to worry about gamete or gonadal preservation before therapy. Although experimental, these techniques have potential in oncofertility.

COSTS OF FERTILITY PRESERVATION

The costs of fertility preservation are unlikely to be covered by insurance,[65] although the psychological distress and effects of infertility are well documented.[66,67] Therefore, patients and their families become responsible for all of the costs. Although some techniques are considered experimental and are, therefore, of unproven benefit, sperm preservation is a technique that has been used for many years and has associated benefits and a record of success that would allow for a change in coverage for this option.

The cost of sperm cryopreservation after masturbation was estimated in 2006 at approximately $1500 for 3 samples stored for 3 years, with additional costs incurred if alternative methods were needed to obtain sperm or for prolonged storage.[35]

The costs of ovarian-tissue preservation can be separated into 3 parts: (1) the procedure to retrieve the tissue, generally laparoscopy and attendant anesthesia[68]; (2) ovarian-tissue pathologic evaluation and freezing; and (3) the annual cost of ovarian-tissue storage. This cost estimate does not include the initial screening and evaluation costs performed before in vitro fertilization or the costs of estradiol testing during therapy (typically 5 blood tests at approximately $200 per sample). Egg retrieval, anesthesia, egg cryopreservation, and the first year of frozen-egg storage costs can be estimated at $5538 (Thomas Toth, MD [Vincent Reproductive Endocrinology Service, Massachusetts General Hospital, Boston, MA] written communication, March 17, 2006). Laparoscopic procedures, even in children, often can be performed on an outpatient basis, precluding any inpatient hospitalization cost.[58] The cost of ovarian-tissue freezing alone might be similar to that of freezing of testicular sperm after testicular dissection (see previous discussion), and the annual cost of ovarian-tissue storage is similar to that of embryo cryopreservation,[50] which costs approximately $350 to $500 per year.[35] Assuming recovery of the patient after treatment, the costs will then include tissue thawing and the procedure for autotransplantation, subsequent medications/hormones, and laboratory testing. The cost of subsequent thawing, culture, fertilization, and embryo transfer followed by 1 pregnancy blood test can be estimated at $3162. Separate costs would include the medication costs necessary for cycling at $2000 to $4000 per cycle, and $330 per ultrasonographic examination. The need for more sophisticated assisted reproduction techniques, such as intracytoplasmic sperm injection, would add additional costs. Use of ovarian suppression with gonadotropin-releasing hormone analogs or antagonists to ovarian tissue during chemotherapy or radiation therapy costs approximately $500 per month.[35]

ETHICAL ISSUES

Fertility preservation raises several ethical issues, including disclosure of the reproductive consequences of therapy, evidence regarding the options for fertility preservation in the setting of available techniques, cultural issues, the consent process,[20,69] and the dilemma of counseling someone who has not yet reached adulthood to make decisions concerning his or her reproductive health while facing the treatment of a life-altering disease.[70] Recognizing that fertility preservation may create both burdens and opportunities for patients with cancer, discussions regarding reproductive potential should take place in the context of maximizing the child's future options and well-being.

Recent surveys of adult male and female cancer survivors of reproductive age and studies evaluating oncology practice patterns for discussing infertility suggest that a conversation with patients with cancer on the infertility consequences of their treatment is lacking in more than half of cases.[35] Some physicians do not recognize the importance of this issue, assume that patients cannot afford fertility-preservation procedures, feel emotionally uncomfortable discussing the topic, or choose not to refer the patient because of the poor prognosis of the tumor.[50]

Most men who completed a survey given by Schover et al[71] felt that having experienced cancer increased the value they placed on family closeness and would make

them better parents. For men who desire children in the future, lack of timely information is the most common reason for not banking sperm. 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.[46] Facilitating the andrology laboratory visit and delaying the induction of chemotherapy, if possible, are 2 approaches that might be used in appropriate cases to increase the fertility options of cancer survivors. Some situations, however, 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.

At the present time, ovarian-tissue preservation is limited to centers that perform research by using this technology, and it is considered experimental.[45,72] Offering the technique might provide some degree of comfort in light of a life-threatening diagnosis, because it offers an optimistic perspective for the future that may conform to a patient-centered philosophy of care. An alternative view is that the technique is not essential to the health and well-being of the child, provides unrealistic expectations because of the hope of survival and subsequent procreation, is ethically problematic, and may pose a significant financial or moral burden on the family. In addition, even offering the option to a vulnerable patient may create an additional burden, especially because refusal might be difficult in light of perceived expectations of the physician or family member. Another concern is that children might not be ready to use stored tissue for several years, and deterioration of the germ cells may occur over time.

With the exception of a heritable cancer syndrome, a history of cancer does not seem to increase the rate of congenital abnormalities or cancer in a man's offspring,[73] although some types of cancer pose a greater relative risk of ovarian or testicular metastasis, including leukemia and lymphoma. The safety of sperm preservation in boys with either of the latter disorders (ie, future risk to any offspring) has not been specifically studied. It has been suggested that patients with leukemia may have decreased sperm motility/function related to their illness.[47] Small studies have suggested a transiently higher rate of aneuploidy after chemotherapy and radiation therapy. The sperm of men before treatment may have poor DNA integrity, although in 1 reported cohort of pediatric cancer survivors, DNA integrity of sperm seemed similar to age-matched controls.[74] Ovarian metastatic involvement has been seen in childhood tumors, such as neuroblastoma, Wilms' tumor, lymphoma, osteosarcoma, Ewing sarcoma, and extragenital rhabdomyosarcoma,[75] and in adult women with breast cancer. In a child or adolescent with 1 of these tumors, there is not a specific contraindication to ovarian-tissue cryopreservation if it is available, but the potential risk of development of a metastatic tumor in the reproductive tract must be considered and fully disclosed to the patient and family before proceeding.[76]

Other issues that should be considered include the special circumstances that might be posed by specific religious beliefs or cultural values that preclude either discussing or allowing assisted reproductive techniques or that condemn masturbation.[65] The parent or guardian will most likely be transferring their beliefs to the clinical situation, and these beliefs may or may not represent the child's current or future interests. Individuals who will later be a partner in a marriage (whether arranged or not) may be adversely affected by decisions that are made for them by the patient's parents or guardians. In some cultures, a person's status in the afterlife may be culturally dependent on their ability to reproduce, which makes discussion of future reproductive options much more important. The condition of shyness may be perceived inappropriately as reticence and, thus, a full discussion of the options may be avoided. One study suggested that adolescent boys may be more successful at masturbation if a parent does not accompany them to the sperm bank.[48] Gay adolescents may decline to be involved because of reluctance to disclose their sexual preferences, although the desire to have children is not limited to heterosexual people.

There are fundamental differences between storing a gamete or ovarian tissue and storing an embryo. Embryo cryopreservation is a technique currently offered only to adults. The use of embryo cryopreservation is much different from ovarian preservation in terms of the product that it creates and the issues that it presents. Its use in children would not only be morally problematic from a procedural viewpoint (ie, is it morally acceptable under any circumstances to subject a minor to oocyte retrieval and in vitro fertilization?), but it also would introduce the ethical dilemma of divergent views about the moral status of a preimplantation embryo. Although not technically precluded, exercising this option would force the adolescent to make a mature decision not only about creating an embryo and choosing a partner or anonymous donor but also about future disposition, including the options of disposal, donation for research, or implantation of the embryo in a surrogate mother in the event of death. These are difficult and deeply unstable decisions for healthy adults with infertility and are likely to pose more difficulties for children with cancer. Other ethical issues include the future role of the partner in the decision-making process about the embryo(s) created in this process and what (if any) role the parent(s) or surrogate of the patient should have, both at the time of consent and for the future of the embryo(s). For the parent of the child, the act of preserving a child's life must take precedence over preservation of the possibility of that child's ability to have children, although the goals of each are intertwined.

Finally, consideration must be given to disposition of the sperm, oocytes, or ovarian tissue (in applicable cases) regardless of whether the child lives or dies.[51,65,77] Any procedure performed should be for the benefit of the child's reproductive future, and this must be addressed in the consent process. If the child lives, a decision must

be made relative to when he or she will have the necessary maturity and moral development to make a personal decision about what to do with the cryopreserved biological material. If the child dies, the parents should not have discretion over the biological material, and it should be destroyed.[78] The role that the child plays in this decision should be clearly defined, and questions must be posed and answered before acquisition of any biological specimen. These issues are not unique, have precedent in case law, and need to be addressed by any person who agrees to the preservation of tissue or gametes.[51]

ROLE OF THE PHYSICIAN

A physician's encouragement is a strong predictor of whether an optional intervention will be considered or conducted by a patient. The gesture 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,[25] although the offer may also raise expectations.[69] Most younger patients with cancer have historically been left with significant anxieties and insufficient information about reproductive issues.[79] Oncologists have a responsibility to inform parents and age-appropriate patients about the likelihood that cancer treatment will permanently affect their fertility.[35] Ideally, the decision about candidacy for fertility preservation will be guided by an institutional policy and shaped by a medical team, including a pediatric oncologist, fertility specialist, ethicist, and mental health professional. Parents of minors and age-appropriate children should be informed of their prognosis in realistic terms. The option of adoption should be discussed. The success rates, costs, and experimental nature of specific assisted reproduction techniques and the acceptability of the option to decline the intervention should also be discussed.[69,80] The fertility specialist should lead an open and detailed discussion about ownership of reproductive tissue and/or a biological specimen in the event of the patient's death or incapacity.

There is no evidence that fertility-preservation options used today directly compromise the success of cancer therapy or adversely affect a survivor's health.[35] Other than hereditary genetic syndromes, large registry studies have also failed to demonstrate an increased risk of genetic abnormalities, birth defects, or cancers in the children of cancer survivors.[73,81] Disclosing this information to patients and families will provide reassurance of the potential value of fertility preservation. For families with hereditary conditions that are risk factors for developing malignancies, the development of preimplantation genetic diagnosis of embryos and prenatal diagnostic techniques may offer a way of minimizing the risk of transmitting cancer genes to offspring. The technique of preimplantation genetic diagnosis is controversial insofar as inherited disorders may be early or late in onset and, thus, may be ethically distinct. Although the onset of disease may be later in life, the American Society of Reproductive Medicine Ethics Committee has stated that it is ethical for couples to choose to screen embryos to avoid having children with high-risk cancers.[82]

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

Evaluation of candidacy for fertility preservation should involve a team of specialists, including a pediatric oncologist and/or radiation oncologist, a fertility specialist, an ethicist, and a mental health professional.

1. Cryopreservation of sperm should be offered whenever possible to male patients or families of male adolescents.
2. Current fertility-preservation options for female children and adolescents should be considered experimental and are offered only in selected institutions in the setting of a research protocol.
3. 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 experimental in nature. In some cases, after such consideration, acting to preserve a child's fertility may be appropriate.
4. Instructions concerning disposition of stored gametes, embryos, or gonadal tissue in the event of the patient's death, unavailability, or other contingency should be legally outlined and understood by all parties, including the patient if possible.
5. Concerns about the welfare of a resultant offspring with respect to future cancer risk should not be a cause for denying reproductive assistance to a patient.

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