

**Plan NOW,
Parent Later**

A GUIDE TO
Fertility Preservation Options
for Males

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■ INTRODUCTION

When a child, adolescent, or young adult is diagnosed with cancer, the patient and their family face a number of overwhelming concerns. First and foremost, the patient and their family are focused on surviving the cancer. The survival rate for childhood cancer is now 80% (Lin et al., 2012) and improved survival rates mean that quality of life once treatment is completed is also important.

All medications and treatments have the potential for short- and long-term side effects. For example, hair loss during treatment is a common short-term side effect; hair typically grows back after treatment is done. Long-term effects of cancer treatment may impact patients for the rest of their lives and may not develop until years after treatment is finished. Every form of treatment has different side effects, and the patient's age, gender, treatment strategy, health prior to treatment, and previous treatments all play into whether a patient experiences a side effect, and the degree of the side effect. Your healthcare team will provide you with education materials and information regarding the potential short- and long-term side effects of your child's treatment.

Many families are concerned that treatment may affect their child's ability to have children as an adult, but most childhood cancer survivors will not struggle with infertility. For those patients who are at risk for infertility due to treatment, there may be options to save fertility. If possible, it is best to explore these options before treatment begins, though some options may be available even after treatment is complete.

Sexual and reproductive health is an uncomfortable topic for many families. When thinking about saving your child's fertility, your family should consider religious and cultural beliefs, financial considerations, and your child's maturity. This handbook is an information guide for your family to use when discussing fertility issues with your oncology healthcare team or with a reproductive healthcare provider. This information may be helpful during or after treatment and as the cancer survivor grows into adulthood.

The doctors caring for children with cancer work hard to lessen the effects of treatment on a child's normal growth and development; all children treated for cancer will respond differently to their treatment.

■ NORMAL PUBERTY

MALES

The testes are the primary reproductive organs in males and are responsible for making hormones that help the body make sperm. Prior to puberty, the testes do not make hormones and sperm. The body starts making the hormone testosterone when puberty begins, usually between the ages of 9 and 16 years. Testosterone is responsible for

many of the changes associated with puberty, such as deepening of the voice, facial hair, enlargement of the penis and scrotum, and sperm production. Men will make testosterone throughout their lives, but as they age the body may make less of it. After puberty, men have the potential to make sperm their entire life. However, men are not able to make sperm if the body is not able to make testosterone.

FEMALES

The ovaries are the primary reproductive organs in females. Immature eggs are present in the ovaries before birth and females are born with all the eggs they will ever have. The body is not capable of making more eggs. During puberty, hormones from the brain send signals telling the ovaries to begin maturing a small number of eggs. In most cycles, one of these eggs will be released each month. If the egg is not fertilized by sperm, a woman will have her period. Estrogen and progesterone are hormones made by the ovaries once a young woman starts puberty. They are also necessary for breast growth and other changes that happen during puberty, such as widening of the hips and pubic and underarm hair growth. Menopause, which typically occurs when a woman is in her 50s, takes place when the ovary no longer contains any eggs. When this happens, the ovaries will no longer produce estrogen and progesterone and the woman will stop having a period.

PREGNANCY

Pregnancy occurs when an egg is fertilized by sperm. This typically occurs during sexual intercourse, but some women may require medical intervention (such as in-vitro fertilization) to have children. Pregnancy cannot occur if a male or female has not yet reached puberty or if the body is not able to make the hormones needed for reproduction.

■ EFFECTS OF CANCER TREATMENT ON MALE REPRODUCTION AND PUBERTY

Children diagnosed with cancer may have problems with fertility later in life. This is a potential long-term side effect of the cancer treatment. The reproductive health of children treated for cancer depends on many factors, including the age at the time of diagnosis, total dose and types of chemotherapies, and the combination of chemotherapy and radiation. Radiation and chemotherapy given together may increase a child's risk for fertility problems.

Other problems children may develop after cancer treatment include:

- precocious puberty: puberty that begins before age 9 years in boys
- delayed puberty: puberty that begins after age 16 years in boys
- arrested puberty: puberty that has started but then stops before completion
- testicular dysfunction
- infertility.

Each child is different and each may respond to cancer treatment differently. Not all survivors will develop these problems. The types of problems that can develop after cancer treatment depend on the types and doses of chemotherapy, radiation, and surgery a child receives. The sections below explain problems that may arise from different cancer treatments.



RADIATION EFFECTS

Children who receive radiation to the brain, abdomen, pelvis, lower spine, or those who receive total body irradiation (TBI) are at the highest risk for fertility problems. The dose of radiation that causes infertility is different for all children because it depends on the child's age and other treatments the child receives.

HEAD AND TBI

Radiation given directly to the brain can cause damage to the pituitary gland that makes hormones that tell the testes to make sperm and are necessary for fertility. TBI damages the pituitary gland, as well as the testes. Therefore, TBI affects hormone production in both the brain and the testes.

Boys who are treated for a brain tumor may have radiation directly to the brain and will be at the highest risk for both infertility (no sperm) and damage to the cells responsible for making testosterone. Brain tumors are typically treated with very high doses of radiation to the tumor itself or the brain after the tumor is removed to prevent the tumor from returning. Doses over 40 Gy used to treat brain tumors will prevent the brain from sending signals to the testes to produce testosterone.

Radiation to the eye, brain, or ears in high doses (≥ 18 Gy) may affect pubertal development, and boys who receive radiation to the head may start puberty early.

PELVIC RADIATION

Males who receive radiation directly to the pelvic region or lower abdomen, including the testes, may also have delayed puberty, precocious or early puberty (puberty that occurs before age 9 in boys), and arrested or stopped puberty.

TESTICULAR RADIATION

Testicular radiation will almost always affect sperm production but the extent of the impact will depend on the total dose of radiation to the testes and the age of the patient when radiation is given.

- Radiation to the testes in the amount of 1–3 Gy will cause sperm production to stop. This may be reversible and sperm production might resume after treatment.
- Radiation to the testes in the amount of 3–6 Gy will cause sperm production to stop which is likely NOT reversible.
- Radiation to the testes in the amount of > 6 Gy will cause an irreversible stop in sperm production.

Boys who receive much higher doses of radiation to the testes may also develop leydig cell problems. Leydig cells are responsible for making the hormone testosterone. Radiation to the testes in the amount of 20 Gy or higher may cause Leydig cells to stop functioning. This can cause infertility and low testosterone levels.

CHEMOTHERAPY EFFECTS

The type and dose of chemotherapy determine which fertility problems occur in children treated for cancer. The medicines most likely to cause fertility problems are called alkylating agents. Your pediatric oncologist will discuss the types of chemotherapy your child may receive.

Chemotherapy drugs most likely to result in fertility problems in any child with cancer include:

Alkylating Agents	Heavy Metals	Nonclassical Alkylating Agents
Cyclophosphamide	Carboplatin*	DTIC (Dacarbazine)*
Ifosfamide	Cisplatin*	Temozolomide (Temodar)*
Nitrogen Mustard		
Procarbazine		
BCNU (Carmustine)		
CCNU (Lomustine)		
Melphalan		
Thiotepa		
Busulfan		

**Less likely to result in infertility in both females and males if given without alkylating agents or heavy metals.*

Males treated for cancer are more sensitive to the effects of alkylating chemotherapy drugs. Higher total doses of alkylating and heavy metal chemotherapy can result in higher levels of testicular dysfunction. Testicular dysfunction is defined by sperm production and includes

- lack of sperm (azoospermia)
- low sperm oligospermia)
- small testes
- delayed pubertal development.

EFFECTS OF SURGERY ON MALE REPRODUCTION

Removal of a testicle may cause infertility (lack of sperm) and hypogonadism (decreased testosterone), especially if the pelvis or testes region are exposed to radiation. Males who have both testes removed will be infertile. Boys who have pelvic surgery, which includes cystectomy (bladder surgery), may experience sexual problems due to the location of the testes near surgery site. Surgery near or on the spine may also cause sexual problems in males.

Boys who have large solid tumors near the prostate, lower back, and testes may need surgery, which can damage the nerves that control penile function and may cause problems starting or maintaining an erection or with the quality of ejaculation. The quality of the ejaculation includes the number of sperm present, the health of the sperm, and the motility of the sperm.

OPTIONS FOR SAVING FERTILITY AT THE TIME OF TREATMENT




There are many options for saving fertility in children diagnosed with cancer, but the use of each option depends on your child's age, the severity of disease at the time of diagnosis, additional medical concerns, and cost. Insurance may not cover any expenses for treatments to save fertility. The barriers to fertility preservation include the need to begin cancer treatment immediately, the cost, obtaining consent during a stressful time, as well as ethical and cultural issues.

Some options for fertility preservation, such as sperm banking, have been performed for decades and are not experimental. There may be research or experimental options available to your child. Experimental means that the safety of the treatment is not known either because no pregnancies in humans have occurred or there have not been enough pregnancies to understand the long-term outcomes of the fertility preservation technique.

NON-EXPERIMENTAL OPTIONS FOR SAVING FERTILITY IN MALE PATIENTS BEFORE AND AFTER PUBERTY

- Shielding of the testes during radiation therapy: a special material (lead) vest is put over the child's testes. This can be done during radiation therapy that does not need to include the testes.
- Moving the testes: one or both testes are surgically moved outside the radiation treatment location, to another area of the body. This must be done prior to radiation therapy. If the testes require radiation therapy this is not an option.



It is important to know that these techniques do not protect against the effects of chemotherapy. Your oncologist and radiation oncologist can tell you if these options are appropriate for your son.

EXPERIMENTAL OPTIONS FOR SAVING FERTILITY IN PATIENTS BEFORE AND AFTER PUBERTY

Testicular tissue cryopreservation is performed in the operating room. A small piece of testicular tissue is removed from one or both testes. The tissue is frozen to be used in the future when the patient is ready to become a parent. If the patient has entered into puberty and the testes are making sperm, the sperm could be removed from the tissue and banked for future use. Sperm production typically starts between 13 and 14 years of age. Patients that have not yet entered into puberty may have testicular tissue frozen for future use. Research is ongoing to develop technology to mature or grow sperm from testicular tissue. This is experimental and untested and there is no guarantee the tissue cryopreservation will be useful in the future. This option should only be performed as part of an Institutional Review Board approved research. Testicular tissue cryopreservation is the only option available for males who have not entered into puberty.

This option requires surgery which should be performed before treatment starts. Insurance may or may not pay for this treatment. In addition to the annual storage fees to keep tissue frozen, there may also be additional fees for laboratory studies, processing, and freezing the tissue. Insurance may not pay for these tests. The billing specialists working with the fertility preservation team will be able to provide you information regarding costs and you should check your individual insurance coverage as well.

OPTIONS FOR SAVING FERTILITY IN PUBESCENT PATIENTS

Sperm banking is an established method of fertility preservation. There have been thousands of successful pregnancies worldwide using this method, even in sperm frozen for decades. Illness, medications, and stress may prevent the body from making sperm. It is possible to bank sperm after the initial dose of chemotherapy, although the sperm count may be low and sperm cells may have been damaged by chemotherapy.

Sperm may be obtained in several different ways. The most common method to obtain sperm for freezing is through masturbation. This is typically done at a reproductive medicine center. Patients may be asked to provide 1–3 samples of semen which will be frozen for future use.

There are other options for retrieving sperm if a young man is not able to masturbate. The most common method is testicular sperm extraction (TESE). This option requires surgery to remove sperm from the testicle. This operation is not offered in most

pediatric oncology centers and cannot be done in prepubertal males. Electroejaculation is another option available if a young man is not able to masturbate and provide a sperm sample. It is typically performed under anesthesia. A small electrical current is applied to the rectum to stimulate an ejaculation. With all three options, the sperm are observed underneath a microscope before freezing to make certain live sperm are stored.

Insurance may or may not cover these options and there are yearly storage fees to keep sperm specially frozen. Additionally, there will be mandatory laboratory tests. Insurance may not pay for these tests. The billing specialists working with the fertility preservation team will be able to provide you information regarding costs as well as check your individual insurance coverage. It is best to ask about coverage and payment rather than assuming that insurance or cost might prevent fertility preservation.

■ REPRODUCTIVE OPTIONS FOR SURVIVORS OF CANCER



Survivors of childhood cancer have several options to have children. Talking with a reproductive specialist may be helpful for adult survivors of childhood cancer who want to have children. Resources exist to offer support, education, financial guidance, and information to survivors of cancer to help them find ways to have children.

Fertile Hope, the American Society of Reproductive Medicine (ASRM), and Livestrong are organizations that can provide support and information for cancer survivors who are dealing with reproductive issues.

The most important thing to remember is to have early fertility testing including an early referral to doctors who specialize in fertility problems.

Male survivors of childhood cancer who have fertility problems after treatment may still be able to have children. Males who froze their sperm before beginning cancer treatment will have it available for use. Other ways include an operation to remove available sperm from the testes, using donor sperm from a sperm bank, and pursuing adoption.



■ SURVIVORSHIP MONITORING

All cancer survivors should have yearly visits that monitor height, weight, and pubertal development. In addition, male survivors may require blood tests to evaluate testosterone and other hormone levels responsible for sexual development. If a child has low testosterone or any other abnormal hormones, he will be referred to a hormone specialist called an endocrinologist.

Other tests should include a bone density test to determine how healthy the child's bones are. If any hormone problems or bone problems are found, the survivor may need to be referred to an endocrinologist who can do further examinations and tests and find the right treatment.

Cancer survivors should have lifelong healthcare visits including screening for reproductive problems and other late effects of cancer. Visiting a survivor clinic yearly can help survivors have the tests and monitoring they need to screen for late effects, including problems with puberty and fertility.

■ HOW TO DECIDE IF FERTILITY PRESERVATION IS RIGHT FOR YOUR CHILD

Fertility preservation is a new field of medicine and there is much to learn, especially about protecting a child or adolescent's ability to have children after cancer treatment. When considering options for fertility preservation, patients and families must be aware that pregnancy may not occur, insurance may not pay for the treatment now or in the future, and the long-term effects of the treatment may not be known for years or even decades.

All experimental options should be done under the supervision of an Institutional Review Board. This is to protect the patient from harm and to make sure that families are not taken advantage of during a particularly stressful time. Families must sign a consent stating they understand the research being done on their child. If the child understands what is happening, he or she should also sign an assent agreeing to the procedure. When the patient turns 18 he or she should sign a new consent.

■ CONSENT

The process of consent may already be familiar to you if your child is about to start or has begun treatment. Consent means that you have been provided information regarding treatment, you understand the treatment, and are in agreement with the treatment plan. Any type of fertility preservation, whether standard of care or experimental, requires the consent of patients over the age of 18. If the patient is younger than 18 and able to understand the proposed procedure, the parent(s) will give permission and the child will assent.

There are several things to consider when giving permission for a minor child:

- The parent(s) are acting in the child's best interest and not just fulfilling their desire to be a grandparent.
- Children should not be coerced into a decision regarding fertility preservation.
- If parents cannot agree on fertility preservation, discussion with the healthcare team, social worker, and religious leader may be requested, as appropriate.
- If family is participating in a research study, they may withdraw from the study at any time.
- Consent should also include what will happen to the tissue if the patient dies.
- The patient will consent for banking of tissue when he turns 18.
- The patient may decide at any time to withdraw from a study.

■ QUESTIONS FOR THE FERTILITY PRESERVATION TEAM

- What experience does the clinic have with pediatric cancer patients?
- Does the doctor know how the proposed cancer treatment will impact my child's future fertility?
- How long is the wait for an appointment?
- What experience does the doctor have with fertility preservation?
- What will the clinic do to provide developmentally appropriate materials for my child?
- If English is not my first language, will consents or an interpreter be available in my native language?
- Is this standard therapy or is it experimental?
- If this is experimental technology, is it part of an Institutional Review Board research protocol?
- What blood tests need to be done before fertility preservation?
- Will fertility preservation significantly delay my child's cancer therapy?
- What are the costs of treatment and associated annual storage fees?
- What will insurance pay?
- Is there assistance to families not able to pay the cost upfront?
- What are the possible side-effects of fertility preservation?
- What is done with the tissue or sperm in the event of my child's death?
- What are other options that my child would have for family building in the future?

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Resources

American Cancer Society

www.cancer.org

ASCO Fertility Preservation Guideline

www.asco.org

Children's Oncology Group Long Term Follow-Up Guidelines

www.survivorshipguidelines.org

Livestrong Fertility

www.livestrong.org/we-can-help/fertility-services/

Oncofertility Consortium

www.myoncofertility.org

Save My Fertility

www.SaveMyFertility.org

Sharing Hope Program

www.fertilehope.com/financial-assistance/index.cfm

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