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Distribution of this handbook is made possible
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■ INTRODUCTION

When a child, adolescent, or young adult is diagnosed with cancer, they and their family face a number of overwhelming concerns. The survival rate for childhood cancer is now 80% (Lin et al., 2012), making quality of life after treatment an important consideration.

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 a patient's age, gender, treatment strategy, health prior to treatment, and previous treatments all play a role in determining whether a patient experiences a side effect, and the degree of the side effect. Your healthcare team will provide patients and families with education materials and information regarding the potential long- and short-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 have problems 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 completed.

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 level. This handbook is an information guide your family can 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 producing hormones that help the body make sperm. Prior to puberty, the testes do not make hormones and sperm. When puberty begins, usually between the ages of

9 and 16 years, the body starts making the hormone testosterone. Testosterone is responsible for many of the changes that happen during puberty, such as deepening of the voice, facial hair growth, enlargement of the penis and scrotum, and sperm production. Men make testosterone throughout their lives, but as they age the body may produce smaller amounts. After puberty, men have the potential to make sperm their entire life. However, if the body is not able to make testosterone, men are not able to make sperm.

FEMALES

The ovaries are the primary reproductive organs in females. Immature eggs are present in the ovaries before birth. Females are born with all the eggs they will ever have, as 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 no pregnancy occurs, 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 takes place when the ovaries stop releasing eggs, which typically occurs when a woman is in her 50s. During menopause, estrogen production dramatically decreases and menstruation stops.

PREGNANCY

Pregnancy occurs when an egg is fertilized by sperm. This typically occurs during sexual intercourse, but some women may require medical treatment (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 FEMALE REPRODUCTION AND PUBERTY

Children diagnosed with cancer may have problems with fertility later in life. This is a potential long term side-effect of cancer treatment. The reproductive health of children treated for cancer will depend on many factors, including the age at the time of diagnosis, total dose and types of chemotherapies, and the combination of chemotherapy and radiation. Sometimes 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 8 years in girls
- delayed puberty: puberty that begins after age 14 years in girls
- arrested puberty: puberty that has started but then stops before completion

- ovarian dysfunction
- premature ovarian failure or menopause
- infertility
- inability to carry a pregnancy to full term.

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 will explain which types of treatments may cause these problems.



RADIATION EFFECTS

Children who receive radiation to the brain, abdomen, pelvis, lower spine, as well as 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 age of the child, and other treatments they receive.

HEAD AND TBI

Radiation given directly to the brain can cause damage to the pituitary gland. The pituitary gland makes hormones that signal the ovaries to make the hormones estrogen and progesterone. If the pituitary gland is damaged, the signals to the ovaries will be affected and the ovaries will not make the right amounts of hormones. This will impact puberty and fertility. Females who receive TBI will also have damage to their pituitary gland.

Radiation to the brain can cause delayed, precocious, or arrested puberty in females. Doses greater than 30 Gy are likely to make it difficult for a woman to become pregnant.

RADIATION TO FEMALE REPRODUCTIVE TRACT

Radiation to the pelvis, abdomen, or spine may damage the uterus or ovaries. Radiation to the uterus can make it more difficult for a woman to carry a pregnancy and increase the risk for miscarriage, premature birth, or having a baby with a low birth weight. Women may also have irregular periods or no periods after receiving radiation to the uterus. Radiation to the uterus may decrease blood flow. The uterus becomes less elastic and may not be able to grow during pregnancy, preventing a woman from being able to carry a child to full term (9 months). Women receiving

more than 5 Gy of radiation to the ovaries or uterus are more likely to experience difficulty becoming pregnant or maintaining a pregnancy.

CHEMOTHERAPY EFFECTS

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

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.*

The combination of chemotherapy and radiation may increase the risk for future fertility problems in females. Other factors that may influence how future fertility is affected includes

- total dose(s) of chemotherapy drugs
- patient's pubertal status at the time treatment begins
- patient's fertility status prior to therapy
- location and total dose of radiation.

Many females who receive chemotherapy may not develop fertility problems immediately. In fact, many females do not experience infertility, even after high doses of chemotherapy. However, the age in which females are diagnosed with cancer and treated may affect future fertility. Every survivor will respond to therapy differently, so your child will need regular check-ups during and after therapy to watch for problems.

Females who are diagnosed with cancer and require a hematopoietic stem cell transplantation (HSCT) may develop infertility from high doses of alkylating agents like cyclophosphamide.

EFFECTS OF SURGERY ON FEMALE REPRODUCTION

Because of the proximity of the bladder to the female pelvic organs, girls who have had pelvic surgery, including cystectomy (bladder surgery), may experience sexual problems like a change, decrease, or loss of sensation to the vagina or painful intercourse. Removing one or both ovaries as part of treatment will affect fertility as well. If both ovaries are removed, she will experience menopause symptoms without replacement of hormones. If her uterus is removed for cancer treatment, she will be unable to carry a pregnancy but still may be able to have a child via a gestational carrier (surrogate) if her ovaries are spared.

Neurosurgery or surgery near the spinal cord may also cause sexual problems in females by damaging the nerves near the ovaries and uterus. This may result in a change, decrease, or loss of sensation to the vagina, or painful intercourse.



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 will depend 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 experimental 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 egg harvesting and freezing, have been performed for decades and are not experimental, though 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 as a result of the treatment, or there have not been enough pregnancies to understand the long-term effects of the fertility preservation technique.

6

OPTIONS FOR SAVING FERTILITY IN PATIENTS BEFORE PUBERTY

Nonexperimental Options

- Shielding of the ovaries during radiation therapy: a special material (lead) vest is placed over the child's uterus and ovaries. This can be done during radiation therapy that does not need to include the uterus or ovaries.
- Moving the ovaries (oophoropexy): one or both ovaries are surgically moved outside the radiation treatment field to another area of the body, usually up in the abdominal cavity. This must be done prior to radiation therapy. If the ovaries or uterus must receive radiation, 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 daughter.

Experimental Options

Cryopreserving, or freezing, ovarian tissue: This requires a surgical procedure in which an ovary or part of an ovary is removed. The tissue containing immature eggs is frozen for your child to use later in life. The tissue may be reimplanted inside the body, depending on the type of cancer and treatments received, or potentially, the eggs could be matured outside of the body and used later through in vitro fertilization. Although current research is promising, maturing the eggs outside of the body has not yet been done successfully in humans.

Cryopreserving requires surgery that should be performed before treatment starts. Insurance may or may not pay for this treatment or the yearly storage fees needed to keep the tissue frozen. Additionally, there will be laboratory tests that need to be completed. 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.

OPTIONS FOR SAVING FERTILITY IN PATIENT AFTER PUBERTY BEGINS

Nonexperimental Options

Oocyte freezing is an established method of fertility preservation. Normally, the ovaries only mature one egg for ovulation in a menstrual cycle. This option requires a female to take hormone medications that will tell her ovaries to mature multiple eggs at once. The eggs are removed surgically and then frozen. When a woman is ready to become pregnant, the eggs are thawed and fertilized with sperm. The embryo can then be put into the uterus. This process might take 2-4 weeks to complete. If cancer treatment needs to start immediately, this is not an option.

Insurance may or may not pay for oocyte freezing. There are yearly storage fees to keep eggs, embryos, and tissue frozen. Additionally, there will be laboratory tests that

need to be completed. 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.

Options with Mixed Results

- Gonadotropin-releasing hormone analogs (GnRHa) are hormones thought to rest the ovaries during cancer treatment. A monthly injection is given to prevent the ovaries from releasing eggs every month. More research is needed to prove if this method preserves fertility in pediatric cancer patients.
- Insurance may cover the monthly injection. The billing specialists can assist you to determine if insurance will cover this treatment.

REPRODUCTIVE OPTIONS FOR SURVIVORS OF CANCER

Survivors of childhood cancer who are at risk for reproductive problems may still have opportunities for having children, including

- natural conception: some survivors will still have the ability to have children naturally, but they may go through menopause earlier because of treatment
- using donated eggs or embryos
- gestational carrier or surrogacy (using another female to carry and deliver a future child)
- using frozen eggs or embryos
- adoption.

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.



SURVIVORSHIP MONITORING

Female cancer survivors who may be at any risk for reproductive problems should have yearly examinations that include height and weight measurement. Survivors should also have close and ongoing examinations of pubertal development to be sure they are progressing normally.

Blood tests may include but are not limited to hormone levels (LH, FSH, Estradiol, AMH). Because hormones can affect bone health and development, other examinations may also include bone density measurements. If any hormone or bone problems are found, the survivor may need to be referred to an endocrinologist (hormone specialist) for further testing and treatment recommendations.

Cancer survivors require lifelong examinations for many reasons, and reproductive health in survivors of childhood cancer is important.

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 an adolescent's or young adult's ability to have children after cancer treatment. When considering options for fertility preservation, 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 to decades.

Experimental fertility preservation 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 is able to understand what is happening, she should also sign an assent agreeing to the procedure. When the patient turns 18 years old 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 the patient if over the age of 18 years. If the patient is younger than 18 years and able to understand the procedure being proposed, 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 simply meeting 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.
- Families participating in a research study 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 or she turns 18 years.
- The patient may decide at any time to withdraw from a study, if she is participating in research.

■ INSURANCE

Insurance coverage for fertility preservation varies from policy to policy. Childhood cancer patients and survivors are not infertile, they are at risk to become infertile later in life, which can be confusing. It is best to ask about insurance coverage before the decision is made about fertility preservation.

There may be charitable organizations in your community to assist with some of the costs of fertility preservation. The oncology social worker or fertility specialist may be available to provide information regarding cost assistance.

■ 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?
- How many successful pregnancies have occurred using this method?
- 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 associated with fertility preservation and the annual storage fees?
- What will insurance pay?
- Is there assistance for families who are not able to pay the cost upfront?
- What are the possible side effects of fertility preservation?
- What is done with the tissue or eggs in the event of my child's death?
- What are other options that my child would have for family building in the future?