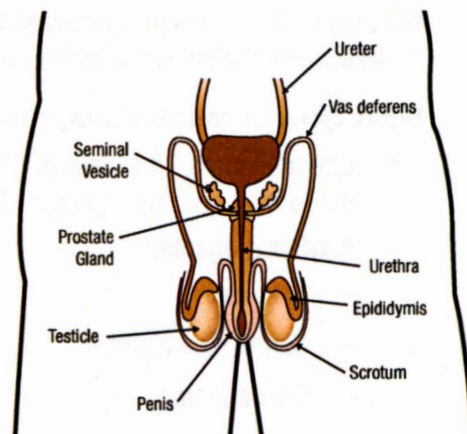


Male Health Issues after Treatment for Childhood Cancer

The effects of childhood cancer therapy on male reproductive function depend on many factors, including the boy's age at the time of cancer therapy, the specific type and location of the cancer, and the treatment that was given. It is important to understand how the male reproductive system functions and how it may be affected by therapy given to treat cancer during childhood.

The male reproductive system

The male reproductive system contains many structures and is controlled by the pituitary gland in the brain. The testicles are located in the scrotum (the loose pouch of skin that hangs behind the penis). The testicles are made up of Leydig cells (cells that produce the male hormone—testosterone) and germ cells (cells that produce sperm). When a boy enters puberty, the pituitary gland in the brain releases two hormones (FSH and LH) that signal the testicles to begin producing sperm and testosterone. As puberty progresses, testosterone causes deepening of the voice, enlargement of the penis and testicles, growth of facial and body hair, and muscular development of the body.



How does cancer therapy affect the male reproductive system?

Cancer therapy can cause **infertility** (the inability to initiate a pregnancy). Infertility can occur following treatment with certain types of **chemotherapy**, **radiation** to the brain or testicles, or **surgery** involving the male reproductive system.

Another possible effect of cancer therapy is **testosterone deficiency**, also known as “hypogonadism” or “Leydig cell failure.” When this occurs, the testicles are unable to produce enough of the male hormone, testosterone. If this happens to a young boy, he will not be able to go into puberty without the help of hormones prescribed by a doctor. If it develops after puberty, a man will need testosterone therapy to maintain muscular development, bone and muscle strength, proper distribution of body fat, sex drive, and the ability to have erections.

What are the causes of male reproductive problems after childhood cancer treatment?

Chemotherapy of the “alkylator” type (such as cyclophosphamide, nitrogen mustard and procarbazine) **may cause infertility**. The total dose of alkylating chemotherapy used during cancer treatment is important in determining the likelihood of damage to sperm-producing cells. The higher the total dose, the more potential for developing infertility. Very high doses can occasionally cause testosterone deficiency. If alkylating chemotherapy was used in combination with radiation, the risk of infertility is increased, and the possibility of testosterone deficiency also exists.

Radiation therapy can affect testicular function in two ways:

- **Radiation aimed directly at or near the testicles.** The sperm-producing cells (germ cells) are very sensitive to the effects of radiation therapy. Most males who receive radiation to the testicles at doses of 3 to 6 Gy (300 to 600 cGy/rads) or higher will be infertile. The testosterone producing cells are more resistant to the effects of radiation and chemotherapy, but if testicular radiation was given in doses of 20 Gy (2000 cGy/rads) or higher, the Leydig cells may stop functioning, resulting in testosterone deficiency (in addition to infertility).
- **Radiation to the pituitary gland in the brain.** Brain radiation can result in damage to the pituitary gland, leading to low levels of the hormones (FSH and LH) needed to signal the testicles to make sperm and testosterone.

Health Link

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Males with low levels of these hormones will need to take testosterone for the rest of their lives. However, it is sometimes possible for these men to regain fertility with the use of specialized hormone treatments. Men who have infertility as a result of brain radiation and wish to achieve fertility should see a fertility specialist.

Surgery that involves removal of both testicles (bilateral orchiectomy) will result in infertility and testosterone deficiency. Pelvic surgery, such as retroperitoneal lymph node dissection (RPLD), or spinal surgery sometimes results in nerve damage that may prevent the ejaculation of sperm. Removal of the prostate or bladder may result in difficulties achieving an erection and/or ejaculation. In these situations, sperm production may be unaffected and fertility may still be possible by using specialized techniques, such as sperm harvesting and artificial insemination. If fertility is desired, consultation with a fertility specialist is recommended.

What types of cancer therapy increase the risk of problems with the male reproductive system?

- Chemotherapy - the class of drugs called “alkylators” can cause infertility when given in high doses. Very high doses may occasionally cause testosterone deficiency. Examples of these drugs are:

Alkylating agents:

- Busulfan
- Carmustine (BCNU)
- Chlorambucil
- Cyclophosphamide (Cytosan™)
- Ifosfamide
- Lomustine (CCNU)
- Mechlorethamine (nitrogen mustard)
- Melphalan
- Procarbazine
- Thiotepa

Heavy metals:

- Carboplatin
- Cisplatin

Non-classical alkylators:

- Dacarbazine (DTIC)
- Temozolomide

- Radiation therapy to any of the following areas may cause infertility.
 - Testicles
 - Pelvis (including iliac/inguinal/femoral, bladder, prostate, total nodal, and “inverted Y” fields)
 - TBI (total body irradiation)
 - Head/brain (cranial)—if dose was 30 Gy (3000 cGy/rads) or higher

In addition to causing infertility, high doses of radiation to the testicles or pelvis (usually 20 Gy or higher) or brain (usually 30 Gy or higher) may also cause testosterone deficiency.

- Surgeries that may cause infertility or disrupt normal sexual functioning include:
 - Removal of both testicles (this surgery will always result in infertility)
 - Retroperitoneal lymph node dissection (RPLD)
 - Removal of tumor in the retroperitoneal area
 - Cystectomy (removal of the bladder)
 - Prostatectomy (removal of the prostate)
 - Spinal surgery
 - Removal of tumor near the spinal cord

In addition, removal of both testicles will result in infertility and testosterone deficiency.

What monitoring is recommended?

Males whose treatment places them at risk for problems with the reproductive system should have a yearly check-up that includes careful evaluation of their hormone and puberty status. Blood may be tested for hormone levels (FSH, LH, and/or testosterone). If any problems are detected, a referral to an endocrinologist (hormone specialist), urologist (specialist in the male reproductive organs) and/or fertility specialist may be recommended. Boys who have had both testicles removed should have regular checkups with an endocrinologist starting at about age 11.

What can be done for testosterone deficiency?

Males with low testosterone levels should receive testosterone replacement therapy. Testosterone is available in several forms, including skin patches, injections, and topical gel. Your endocrinologist will determine which form of therapy is best for you.

How will I know if I am infertile?

Infertility is not related to sexual function. Some men with infertility may notice a decrease in the size or firmness of the testicles, but in others, there are no physical indications of infertility.

Males who had surgical removal of both testicles will not be able to make sperm, and infertility will be permanent. In other males, the only certain way to check for sperm production is to have a semen analysis performed. This test checks the appearance, movement and concentration of sperm in the semen. A semen analysis that shows azoospermia (no sperm in the semen sample) on more than one sample is an indicator of infertility.

Sterility following radiation is likely permanent. However, recovery of sperm production may occur months or years after the completion of chemotherapy in some men. For others, chemotherapy damage may be permanent. It is not possible to determine if sperm production will resume, especially if chemotherapy ended only a few years prior to the semen analysis. For this reason, **always assume that you can make someone pregnant unless you are absolutely sure that you cannot!!**

When should I get a semen analysis?

Any sexually mature male who is concerned about fertility should have a semen analysis performed. Most hospitals with adult services will be able to perform a semen analysis. Not all insurance companies cover the cost of this analysis, so you should check with your insurance company to be sure, or check with the hospital or clinic regarding the costs of this procedure. If the semen analysis results are within normal limits, natural conception can occur.

What if the sperm count is low?

If the results show no sperm (azoospermia) or very low sperm counts (oligospermia), the test should be repeated several times. Sperm recovery following chemotherapy may take as long as 10 years, so if you have had chemotherapy that may cause low sperm counts, it may be important to check periodically over several years. Also, men's sperm counts vary considerably from day to day, so sub-normal test results may improve if additional samples are checked after waiting a month or two. Sperm production and quality may continue to improve as more time passes from the chemotherapy treatment.

Men who have low sperm counts cannot rely on this to prevent pregnancy. Pregnancy can occur with low sperm counts. **Some method of birth control must be used if pregnancy is not desired.**

If pregnancy is desired, men with low sperm counts may benefit from assisted reproductive techniques such as Intra-Cytoplasmic Sperm Injection (ICSI), a form of in vitro fertilization. A consultation with an infertility specialist is helpful in order to obtain further information regarding these options.

What are my options if there are no sperm in the semen analysis?

If semen analysis shows no sperm (azoospermia), and children are desired, a consultation with a doctor who specializes in male infertility should be obtained. Medical advancements dealing with male infertility are being made. Recently, surgeons have been able to locate areas of active sperm production in the testes of men who have no sperm on semen analysis. Surgical harvesting of the sperm has resulted in pregnancies with techniques devised for men with absent or very low sperm counts. *Occasionally, azoospermia may be unrelated to chemotherapy altogether, and treatment for another disorder may be indicated.*

Other good options for males who produce no sperm include donor insemination or adoption. Donor insemination (DI) uses sperm from another male, either from a known or anonymous donor. DI results in pregnancy with a child that is biologically related only to the mother. Additional options may include adoption of a biologically unrelated child or child-free living.

How do I use the sperm cryopreserved before treatment started?

Options for using banked sperm depend on the amount and quality of material saved. Men who banked sperm prior to cancer treatment will need to work with a doctor specializing in reproductive medicine, so that the cryopreserved (frozen) sperm can be used in an optimal manner.

What if only one testicle was surgically removed?

Although fertility and testosterone production are not usually affected if only one testicle was surgically removed, you should take precautions to protect the remaining testicle from injury by always wearing an athletic supporter with a protective cup when participating in any activities that may potentially cause injury to the groin area (such as contact sports, baseball, etc.). If your remaining testicle was treated with radiation, or if you received chemotherapy that can affect testicular function, the effects of these treatments are the same as discussed above.

What are the risks if pregnancy occurs after childhood cancer treatment?

Fortunately, in most cases, there is no increased risk of cancer or birth defects in children born to childhood cancer survivors. In rare cases, if the type of cancer in childhood was a genetic (inherited) type, then there may be a risk of passing that type of cancer on to a child. You should check with your oncologist if you are not sure whether the type of cancer you had was genetic.

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Additional health information for childhood cancer survivors is available at
www.survivorshipguidelines.org

Note: Throughout this *Health Links* series, the term "childhood cancer" is used to designate pediatric cancers that may occur during childhood, adolescence, or young adulthood. Health Links are designed to provide health information for survivors of pediatric cancer, regardless of whether the cancer occurred during childhood, adolescence, or young adulthood.

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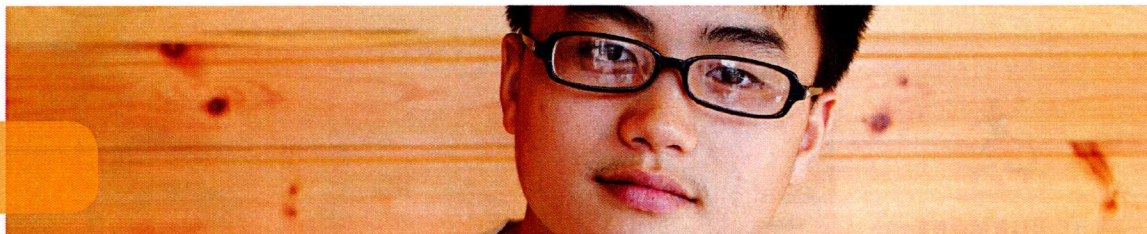
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Testicular Tissue Cryopreservation Study

- The treatment your son will receive has a damaging effect on the stem cells in his testes. As a consequence, he is at high risk to not be able to produce sperm later on.
- This study is being done because at this time there are no other options for boys to preserve their fertility before reaching puberty and being able to freeze sperm.
- In this study, a small piece of tissue (biopsy) will be removed from one testicle, and the tissue will be frozen. The stem cells in the testis can later be transplanted back into the testis and we hope they will be able to produce sperm.
- The study is experimental and no testicular tissues or cells have been transported back to humans at this time. Studies have been conducted in animals, including monkeys, and it is looking promising to restore sperm production for men in the future. There are a lot of unknowns, but given that your son is young, there is a lot of time for technology and research to advance. The idea is to store germ cells and hopefully restore sperm production to be used in the future with advanced fertility techniques.
- The surgical procedure is done by one of our pediatric urology surgeons. It is done under general anesthesia, so your son will be completely asleep. The surgeon will then take a portion of one testicle. The surgery itself is less than a half an hour. A small portion is sent to pathology to make sure that it is normal healthy testicular tissue.
- The tissue is then transported to Magee-Womens Hospital of UPMC in Pittsburgh PA where it is processed and frozen. A small portion will go to research and the remainder will be stored for your son's personal use.
- The study will pay for processing of the tissue, transport of the tissue to long term storage and first year of storage. After that you are responsible for the annual storage fees for the tissue.
- The recovery time is minimal. It is done as an outpatient procedure, so you will not stay overnight in the hospital.
- Please review the study consent in detail



What are the options for fertility preservation?

Your child's doctor may refer you to a fertility specialist to discuss fertility-saving treatments. Treatment options depend on whether your child has gone through puberty. Children who have reached puberty have more **options to save their fertility**. Most girls start puberty between ages 8 and 13 years. Most boys start producing sperm by age 13.

Options for boys after puberty include:

- **Sperm banking.** Freezing (cryopreservation) of sperm is the most successful way to preserve fertility before cancer treatment. The most common way to collect the semen (the fluid carrying sperm) is through masturbation. Boys who cannot ejaculate (eject semen from the penis) may have vibrational or electrical stimulation to help them do so. The sperm stay frozen, or "banked," until needed. Freezing—even for many years—does not damage sperm.
- **Testicular sperm extraction.** Even if a boy's semen has no sperm, he may still have sperm in the testicles. In testicular sperm extraction, a surgeon removes small pieces of testicular tissue while the boy is sedated or under local or general anesthesia. If the tissue contains sperm, the sperm are removed and frozen. This technique may be an option before or after cancer treatment.
- **Shielding of testicles during radiation therapy.** It is sometimes possible to shield the testicles to protect them from radiation during treatment.
- **Testicular tissue freezing.** Some clinics are testing this experimental method. It involves removing and freezing small pieces of testicular tissue before cancer treatment. This tissue may be re-implanted in the future, but so far, no children have been born using this method.

Your child's doctor may refer you to a fertility specialist.

Options for girls after puberty include:

- **Pelvic shielding during radiation therapy.** It may be possible to shield one or both ovaries to protect them from radiation during treatment.
- **Ovarian transposition.** Before radiation treatment to the pelvic or spinal region, a surgeon moves one healthy ovary, or both, to another spot in the girl's body outside the treatment field.
- **Egg banking.** This experimental method involves freezing and storing unfertilized eggs. It usually requires fertility drugs and monitoring with ultrasounds and blood work for about 2 weeks. This could delay the start of cancer treatment and may not be an option for some girls. Banking embryos (fertilized eggs) is an option if a girl is willing to use sperm from a partner or a sperm donor to fertilize the eggs. However, this not a common treatment for adolescent girls. It also requires about 2 weeks of fertility drugs.
- **Ovarian tissue banking.** This experimental method involves removing small pieces of an ovary and storing the tissue frozen. A surgeon may be able to re-implant the tissue after cancer treatment. This may not be a safe option for girls with leukemia because there could be cancer cells in the tissue. The tissue might also be used to mature the follicles and enclosed eggs and fertilize the eggs outside of the body, but no children have been born using this technique yet.

Before puberty, children have fewer options because they do not yet make sperm or mature eggs. Their only options to preserve fertility are shielding during radiation therapy, freezing tissue from the reproductive organs (ovaries or testicles), or ovarian transposition for girls.



How does cancer treatment in young children affect puberty?

Because of cancer treatment, children may be at risk for early or delayed puberty.

Early, or “precocious,” puberty is any physical sign of **sexual maturity** before the age of 9 in boys and age 8 in girls. This may occur after radiation to the brain. Radiation can cause early release of hormones from the brain that signal the body to start puberty.

Puberty is delayed when it has not started by age 14 in boys or 13 in girls. This may also occur from radiation to the brain, or if treatment harms the testicles or ovaries so they cannot produce sex hormones.

Being ahead of or behind their peers in sexual maturity may cause some children to have emotional or social adjustment problems.

What are the treatments for early or late puberty?

To treat early puberty, medicines can stop the release of sex hormones. Treatment most often is stopped when the child reaches the normal age of puberty.

Children with delayed puberty may receive treatment with estrogen (girls) or testosterone (boys) to help bring about normal signs of puberty.

What should you do with this information?

Your child’s doctors may not raise the topic of fertility preservation or how cancer treatment can affect puberty. You should raise the issue if you have concerns. Here are some questions to ask the doctor:

- How quickly does my child need to start cancer treatment?
- Will cancer or its treatment affect my child’s future fertility?
- What are my child’s options to preserve fertility?
- What are the success rates for each option?
- Will my medical insurance cover the cost of these procedures?
- Is my child at risk for early or delayed puberty?

Resources

Save My Fertility
SaveMyFertility.org

Fertile Hope
www.fertilehope.org

Find-an-Endocrinologist
www.hormone.org/FindAnEndo/index.cfm

American Society for Reproductive Medicine
www.asrm.org/patient_resources

The Hormone Foundation
www.hormone.org

KidsHealth
kidshealth.org

Oncofertility Consortium
myoncofertility.org
oncofertility.northwestern.edu or call
1-866-708-FERT (1-866-3378)

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The Hormone Foundation®, the public education affiliate of The Endocrine Society®, serves as a resource for the public by promoting the prevention, treatment, and cure of hormone-related conditions through outreach and education.

The Oncofertility Consortium® is a national, interdisciplinary initiative designed to explore the reproductive future of cancer survivors.

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