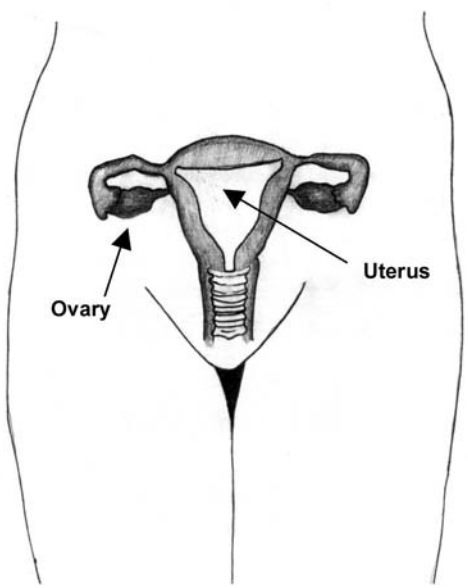
Female Health Issues after Treatment for Childhood Cancer

The effects of childhood cancer therapy on female reproductive function depend on many factors, including the girl'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 ovaries and female reproductive organs function and how they may be affected by therapy given to treat cancer during childhood.

The female reproductive system

At birth, the ovaries contain all the eggs they will ever have. When the time comes to begin puberty, the pituitary gland in the brain signals the ovaries by releasing two hormones (FSH and LH). The ovaries secrete the female hormones estrogen and progesterone, which are necessary for reproductive function. Normally, during a monthly menstrual cycle, one egg matures and is released from the ovaries. If the egg is not fertilized, menstruation begins. The cycle then repeats itself about every 28 days. With each menstrual cycle, the supply of eggs decreases. When most of the eggs are depleted from a woman's ovaries, menopause begins. During menopause, the menstrual cycles stop, the ovaries stop making hormones, and the woman is no longer able to become pregnant.



How does cancer therapy affect the ovaries?

Certain chemotherapy drugs, radiation therapy, and surgery can sometimes damage the ovaries, reducing the reserve supply of eggs. When the ovaries are not able to produce eggs or hormones, this is called **ovarian failure**.

What are the causes of ovarian failure?

Chemotherapy of the "alkylator" type (such as cyclophosphamide, nitrogen mustard and busulfan) is most likely to affect ovarian function. The total dose of alkylators used during cancer treatment is important in determining the likelihood of ovarian damage. With higher total doses, the likelihood of damage to the ovaries increases. If treatment

for childhood cancer included a combination of both radiation and alkylating chemotherapy, the risk of ovarian failure may also be increased.

Radiation therapy can affect ovarian function in two ways:

Primary (direct) failure of the ovaries can be caused by radiation that is aimed directly at or near the ovaries. The age of the person at the time of radiation and the total radiation dose can affect whether or not ovarian failure occurs. Generally, younger girls tend to have less damage to the ovaries than people who received equal doses but who were teenagers or young adults at the time of radiation. However, higher doses usually cause the ovaries to stop functioning in most females regardless of age.

Secondary (indirect) failure of the ovaries can occur as a result of radiation therapy to the brain. The pituitary gland, located in the center of the brain, regulates the production of two hormones (FSH and LH) needed for proper ovarian function. Radiation to the brain at higher doses can damage the pituitary gland, leading to low levels of these hormones.

Surgery. If both ovaries were removed (bilateral oophorectomy) during cancer therapy, this always results in ovarian failure. This type of ovarian failure is sometimes called "surgical menopause". If one ovary was removed (unilateral oophorectomy), menopause may occur earlier than it otherwise would have ("premature menopause").

What types of cancer therapy increase the risk of ovarian failure?

Females who received the following therapy may be at risk for ovarian failure:

- **Radiation therapy** to any of the following areas:
  - Whole abdomen
  - Pelvis
  - Lower spine (lumbar and sacral areas)
  - Total body (TBI)
  - Head/brain (cranial) – if dose was 40 Gy (4000 cGy/rads) or higher

- **Chemotherapy** - the class of drugs called "alkylators" can cause ovarian failure when given in high doses. Examples of these drugs are:

  Alkylating agents:
  - Busulfan
  - Carmustine (BCNU)
  - Chlorambucil

- Cyclophosphamide (Cytoxan®)
- Ifosfamide
- Lomustine (CCNU)
- Mechlorethamine (nitrogen mustard)
- Melphalan
- Procarbazine
- Thiotepa

Heavy metals:
- Carboplatin
- Cisplatin

Non-classical alkylators:
- Dacarbazine (DTIC)
- Temozolomide

- **Surgery:**
  - Removal of one or both ovaries

What are the effects of childhood cancer therapy on the female reproductive system?

1. Failure to enter puberty. Pre-pubertal girls who received cancer therapy that results in ovarian failure will need hormonal therapy (hormones prescribed by a doctor) to progress through puberty. If this occurs, referral to an endocrinologist (hormone doctor) should be made for further evaluation and management.

2. Temporary cessation of menstrual cycles. Many females who were already menstruating will stop having monthly periods during their cancer therapy. In most cases, menstrual cycles will resume sometime after cancer treatment ends, although the timing of this is unpredictable. In some cases, it may take up to several years to restart menstruation. Since eggs are released before the menstrual cycles, pregnancy can occur before the menstrual periods resume. ***If pregnancy is undesired, birth control (contraception) should be used, even if the menstrual cycles have not resumed.***

3. Permanent cessation of menstrual cycles (premature menopause). Menopause (the permanent cessation of menstrual cycles) occurs at an average age of 51. Females who were already menstruating prior to their cancer therapy sometimes develop ovarian failure as a result of their cancer treatment and never resume menstrual cycles. Others may resume menstrual cycles, but then stop menstruating much earlier than would normally be expected. If a woman is currently having menstrual periods

but received chemotherapy or radiation that can affect ovarian function or had one ovary removed, she may still be at risk for entering menopause at an early age. ***If a woman at risk for premature menopause desires to have children, it is best not to delay childbearing beyond the early thirties, because the period of fertility may be shortened after having cancer therapy.***

4. Lack of female hormones. Females with ovarian failure do not make enough estrogen. Estrogen is needed for functions other than reproduction – it is very important for maintaining strong healthy bones, a healthy heart, and overall well-being. Young women with ovarian failure should see an endocrinologist (hormone specialist) for hormone replacement therapy, which will be necessary until they reach middle age.

5. Infertility. Infertility is the inability to achieve a pregnancy after at least one year of unprotected intercourse. In women, infertility occurs when the ovaries cannot produce eggs (ovarian failure), or when the reproductive organs are unable to sustain a pregnancy. Infertility may be the result of surgery, radiation therapy, chemotherapy, or any combination of these. *There may also be other reasons for infertility that are unrelated to cancer therapy.*

If a woman has regular monthly menstrual periods and normal hormone levels (FSH, LH and estradiol), she is likely to be fertile and able to have a baby. If a woman does NOT have monthly menstrual periods, or if she has monthly menstrual periods ONLY with the use of supplemental hormones, or if she had to take hormones in order to enter or progress through puberty, she is likely to be infertile.

Girls who had surgical removal of both ovaries will be infertile. Girls who had surgical removal of the uterus (hysterectomy) but still have functioning ovaries can become mothers with the use of a gestational surrogate (another female who carries the pregnancy to term). Women who are infertile should discuss their options with a fertility specialist and their oncologist. The use of donor eggs may be an alternative for some women. Additional options may include adoption of a biologically unrelated child or child-free living.

6. Pregnancy risks. Certain therapies used during treatment for childhood cancer can sometimes increase the risk of problems that a woman may experience during pregnancy, labor, and childbirth. The following women may be at increased risk:

- Women who had radiation to the whole abdomen, pelvis, lower spine, or total body (TBI) may have an increased risk of miscarriage, premature delivery, or problems during labor.

- Women who received anthracycline chemotherapy (such as doxorubicin or daunorubicin), and women who received radiation to the upper abdomen or chest may be at risk for heart problems that can worsen with pregnancy and labor (*see related Health Link: "Heart Health"*).

Women with these risk factors should be followed closely by an obstetrician who is qualified to care for women with high-risk pregnancies.

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.

What monitoring is recommended?

Females who have had any of the cancer treatments that may affect ovarian function should have a yearly check-up that includes careful evaluation of progression through puberty, menstrual and pregnancy history, and sexual function. Blood may be tested for hormone levels (FSH, LH, and estradiol). If any problems are detected, a referral to an endocrinologist (hormone specialist) and/or other specialists may be recommended. For women with ovarian failure, a bone density test (special type of x-ray) to check for thinning of the bones (osteoporosis) may also be recommended.

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Health Link

Healthy living after treatment for childhood cancer

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.