

Fertility Nurses First

Fertility preservation in women with cancer: FAQs

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Fertility preservation is one of the most important issues in women diagnosed with cancer, as aggressive cancer treatment can cause premature ovarian failure. Most women of reproductive age wish to preserve fertility, but either: 1) fail to receive adequate information about fertility preservation or 2) fail to be referred to fertility specialists when appropriate. This article is intended to propagate knowledge and awareness of fertility preservation for healthcare professionals, as well as the general public. Below are common FAQs that are worth exploring.

Q. Will any cancer treatment result in infertility in young women of reproductive age?

A. Although most chemotherapeutic agents and ionized radiation are gonadotoxic, the severity of toxicity varies. For example, some agents, such as doxorubicin, 5FU or methotrexate are less toxic to the human ovary compared to alkylating agents, such as cyclophosphamide or busulfan. Radiation damage to the ovary with pelvic irradiation or total body irradiation (TBI) can cause a significant loss of follicles. In addition, almost all patients older than age 10 receiving over 15Gy of TBI will develop premature ovarian failure.

Q. Does age at the time of cancer diagnosis impact fertility after cancer treatment?

A. Age is one of the most important prognostic factors in those with cancer who wish to conceive. The chance of maintaining fertility after cancer therapy is much higher in women under age 30 compared with those over age 30. The number of oocytes in the ovaries gradually declines with age, while the ovarian reserve decreases significantly after age 35. Insult to the ovary with cancer treatment can further reduce the ovarian reserve.

Q. How common is cancer diagnosis in women of reproductive age?

A. In the United States, 4 percent to 5 percent (55,000/year) of newly diagnosed cancer patients are under age 35.¹ Five percent to 7 percent (11,000/year) of patients diagnosed with invasive breast cancer are under age 40. In addition, there are approximately 450,000 cancer survivors who are of reproductive age.

Q. Have cancer survival rates improved in young cancer patients?

A. Many types of cancer are curable if detected in the early stages. Survival rates have increased over the past 20 years thanks to advances in cancer treatment. The 5-year relative survival rate for all cancers combined is more than 83 percent in women aged 15 to 44.² For children aged 0 to 14, the overall 5-year relative survival rate is more than 81 percent in the United States. The survival rate for Hodgkin's disease in the pediatric population is more than 95 percent. Long-term relative survival rates are greatest among women aged 20 to 29 years when compared to other age groups.

Q. Before undergoing cancer treatment, are women concerned with fertility?

A. Infertility due to cancer therapy can cause significant psychological stress and directly influence the quality of life of cancer survivors. At least 75 percent of young women, without children at the time of cancer diagnosis, desire to have children in the future. Among adolescent girls diagnosed with cancer, 80 percent of them are interested in fertility preservation.³ In addition, cancer survivors prefer to have their own biological children.

Q. Do most women of reproductive age receive adequate information about fertility preservation before cancer treatment?

A. Less than half of the oncologists in the United States are following fertility guidelines pertaining to patient recommendations from the American Society of Clinical Oncology (ASCO).⁴ These guidelines recommend oncologists to discuss fertility issues with patients of childbearing age and make referrals to reproductive specialists and psychosocial providers as appropriate. In addition, more than half of young women are not being given adequate fertility information by their physicians or referred to fertility specialists when needed.

Q. What are significant barriers for fertility preservation?

- A. For patients who desire fertility preservation before cancer treatment, there are two main barriers:
1. *Lack of referral to fertility specialists in a timely manner:* Women diagnosed with cancer should be given an opportunity to preserve their fertility via referrals to fertility specialists. Incomplete or incorrect provider knowledge about fertility preservation may hinder timely referrals—especially in cases where treatment should be immediate.⁵
 2. *Expensive treatment:* Most procedures for fertility preservation are not covered by health insurance. This can be a challenge—especially in cases where cancer treatment should be initiated immediately. In addition, restoration of fertility cannot be guaranteed.

Q. What are the currently available options for fertility preservation?

- A. They are the following⁶:
- Gonadotropin-releasing hormone agonists (GnRHa)
 - Oophoropexy (for pelvic irradiation)
 - Controlled ovarian stimulation (COS) with cryopreservation of mature oocytes or embryos
 - Cryopreservation of immature oocytes or *in vitro* maturation followed by cryopreservation of mature oocytes
 - Cryopreservation of ovarian tissue
 - Donor egg *in vitro* fertilization (IVF)
 - Surrogacy
 - Adoption

Q. Who are ideal candidates for hormonal protection with GnRHa co-treatment?

A. Although numerous trials show GnRHa to protect ovarian function from chemotherapy-induced gonadotoxicity, results from these published studies are neither consistent nor convincing, mainly due to suboptimal study designs and inadequate sample sizes.⁷ It may be reasonable to consider GnRHa co-treatment when there are no other options due to patient conditions/time factors. It is important to note that GnRHa does not protect the ovary from radiation-induced gonadotoxicity.

Q. What is considered when counseling patients undergoing GnRHa treatment?

A. Because efficacy of GnRHa treatment remains controversial, it is important to inform patients of the side effects including osteoporosis and various menopausal symptoms. GnRHa treatment should start before chemotherapy, or at the time of chemotherapy, and continue until after the end of chemotherapy to maximize the protective effects. Currently, GnRHa treatment is not recommended for breast cancer patients with estrogen receptor-positive (ER+) status.

Q. Are there any clinically established technologies among fertility preservation strategies?

A. Most fertility preservation options for women diagnosed with cancer are considered to be investigational, with the exception of embryo cryopreservation. Embryo cryopreservation has shown positive results for approximately 30 years. The current live birth rate per transfer is around 36 percent in women younger than 35 years of age. Although oocyte cryopreservation is still considered investigational,

current live birth rates from a series of cryopreserved oocytes are comparable to those in cryopreserved embryo transfer cycles—especially if those cryopreserved oocytes have undergone vitrification (a freezing method that requires a high concentration of cryoprotectants along with an extremely high cooling rate).

Q. Is embryo cryopreservation applicable to all women with cancer?

A. As the process of embryo cryopreservation takes two to five weeks, it may not be applicable to patients who require immediate cancer treatment. In addition, this process is not practical for patients without partners or who do not want to use donor sperm. Furthermore, gonadotropins (the main agent for COS) increase peak estradiol levels, which may be contraindicated in patients with breast cancer—especially those with ER+ status.

Q. What is the process of embryo cryopreservation?

- A. Patients need to undergo the following:
1. IVF procedure that includes COS with gonadotropins for 10 to 14 days
 2. Monitoring of follicular growth with ultrasound and blood tests during COS
 3. Oocyte retrieval about 36 hours after hCG administration
 4. Fertilization of retrieved oocytes with sperm using IVF or intracytoplasmic sperm injection

Q. Is it safe to use gonadotropins to stimulate the ovaries for embryo preservation in breast cancer patients?

A. COS with gonadotropins most likely increases serum estradiol levels to supra-physiologic amounts. This poses a concern to breast cancer patients as high levels

of estrogen can stimulate cancer cell proliferation. To minimize the risk of exposure to high estrogen amounts, the use of tamoxifen or letrozole instead of gonadotropins has been suggested, although their use does not generate sufficient numbers of follicles for embryo cryopreservation. Another recommendation is to use a modified protocol that comprises low-dose gonadotropin in combination with tamoxifen or letrozole.⁸ Although the safety and efficacy of this protocol is being further studied, results are satisfactory regarding the number of retrieved oocytes, fertilization rates and serum estradiol levels.

Q. What are the indications for oocyte cryopreservation?

A. Oocyte cryopreservation is an alternative strategy to embryo cryostorage, and is ideal for women who do not have a partner and do not want to use donor sperm. It also can be a suitable option for women who do not want to create embryos for storage. This procedure requires COS and egg retrieval—the same process required for embryo cryopreservation. Oocyte cryopreservation, however, does not require IVF.

Q. Is oocyte cryopreservation as successful as embryo cryopreservation?

A. To date, more than 1,000 healthy babies have been born worldwide through the process of oocyte cryopreservation.⁹ Although human oocytes can be cryopreserved using a slow freezing method, cryopreservation has been more successful using vitrification. Live birth rates per embryo transfer with embryos resulting from vitrified oocytes are comparable to those in frozen-thawed embryo transfer cycles (approximately 35 percent).

Q. To whom can ovarian tissue cryopreservation be offered?

A. Ovarian tissue cryopreservation is the only option for: 1) pre-pubertal girls 2) patients who cannot delay cancer treatment or 3) patients who are unwilling to undergo COS. Patient age is crucial as the chances of restoration of ovarian function and fertility are closely correlated to the number of follicles in the ovarian tissue (which declines with age). In general, it is not recommended to cryopreserve ovarian tissue if the patient is older than age 38.

Q. What are the main advantages of ovarian tissue cryopreservation when compared to embryo or oocyte cryopreservation?

A. The main advantages of ovarian tissue cryopreservation are the following:

1. It can permanently store abundant amounts of immature oocytes for future use.
2. It can restore fertility as well as endocrine function after ovarian tissue transplantation.
3. It does not delay cancer treatment.
4. It does not increase serum hormone levels.

Q. What are disadvantages of ovarian tissue cryopreservation?

A. Because this is an invasive procedure, surgical complications can occur. The ovary is usually harvested by laparoscopic surgery. When the patient is ready to have a child, she may need another surgery to transplant frozen-thawed ovarian tissue back to her own body.

Q. How is ovarian tissue harvested and processed?

A. The ovary can be harvested using laparoscopic surgery under general anesthesia. It takes approximately one hour to complete surgery. Most times, cancer therapy can be resumed three to seven days after surgery. The harvested ovary is processed into thin sections of ovarian cortical tissue (5 mm x 5 mm x 1 mm) before cryopreservation.

Q. Is it safe to transplant stored ovarian tissue from cancer patients?

A. Although rare, ovarian tissue can harbor cancer cells—especially in cases of hematologic malignancy, such as leukemia.¹⁰ Awareness and recognition of the risks of reintroduction of cancer cells are crucial for the safety of ovarian tissue transplantation. To date, over 50 cases of ovarian transplantation have been successfully performed in women with no documented cases of cancer cell reintroduction. Cases include women with various cancers, such as breast cancer, cervical cancer, Hodgkin’s lymphoma, non-Hodgkin’s lymphoma and Ewing sarcoma. Despite these results, safety concerns for this procedure will remain until reliable screening methods to detect minimal residual disease in ovarian tissue are developed.

Q. How many babies have been born after transplanting frozen-thawed ovarian tissue?

A. Although controversial, transplantation of frozen-thawed ovarian tissue has been shown to restore fertility in humans. As of June 2011, this technology has been responsible for 15 healthy live births and two ongoing pregnancies worldwide.¹¹ Despite these results, the clinical efficacy of this technology is being further investigated.

Q. To summarize, what are the main points of fertility preservation in young women diagnosed with cancer?

- A. They are as follows:
1. Most women of reproductive age desire to preserve fertility in order to have a family in the future.
 2. It is important to address fertility issues when counseling the patient, preferably immediately after cancer diagnosis.
 3. In general, there is not much time between the time of cancer diagnosis and treatment. If fertility preservation is desired, it is recommended to refer the patient to a fertility specialist once a cancer diagnosis is made.
 4. Strategies for fertility preservation should be carried out based on each individual patient case, taking into account diagnosis, treatment, age, marital status, etc.

About the author:

S. Samuel Kim, MD is an internationally renowned specialist in reproductive endocrinology and infertility. He has contributed to the advances of fertility preservation as a pioneer in ovarian tissue cryopreservation and transplantation, and his seminal work in fertility preservation has been recognized worldwide. Dr. Kim currently serves as president of the International Society for Fertility Preservation.

Dr. Kim completed his resident training at Temple University in Philadelphia and fellowship at the University of Washington in Seattle. In addition, he completed a post-doctoral research fellowship at the University of Leeds in England. Currently, Dr. Kim is head and associate professor of the Division of Reproductive Endocrinology at the University of Kansas (KU) School of Medicine. He is also the director of the Fertility Preservation Program at the KU Cancer Center.

Dr. Kim has authored several published works in numerous prestigious journals and medical textbooks including *Nature and Principles and Practice of Fertility Preservation*. Throughout his career, Dr. Kim has received various scientific awards and has lectured around the world.

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