For women

Preserving fertility before cancer treatment

For young women with cancer
who wish to have children in the future

What is fertility?

Fertility is defined as "the ability to reproduce".
Cancer treatment may affect your reproductive functions, but there are many fertility preservation options available.

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Introduction

Recent advances in cancer treatment have aided many in overcoming cancer. Yet, despite these advances, some treatments can affect ovarian function, which may lead to infertility. It is therefore important to understand the potential impact of cancer treatment on reproductive health when considering one's options for fertility preservation.

This brochure will assist young female patients in making informed decisions about their fertility preservation options.

Fertility Preservation Checklist

- [ ] **1.** I understand the process and prospects of cancer treatment, and how they may affect my fertility.
- [ ] **2.** I understand my fertility preservation options and what they involve.
- [ ] **3.** I understand the commitment and costs of fertility preservation as well as its potential effect on my cancer treatment.
- [ ] **4.** After cancer treatment, pregnancy will be permitted only if my oncologist finds the conditions fitting.
- [ ] **5.** I should consult my oncologist and reproductive endocrinologist about my fertility preservation options.
- [ ] **6.** I understand that fertility preservation does not guarantee future pregnancy.

It is important to discuss all of these points with your partner, family, and any others who may be affected by your decision.

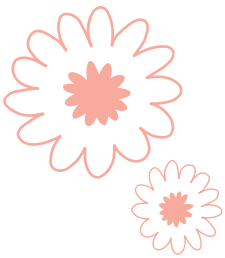
Cancer treatment and fertility preservation

Prioritizing cancer treatment over fertility preservation

Starting an appropriate cancer treatment regimen is of utmost importance. Although fertility preservation may be an important consideration, proper cancer treatment should be prioritized over family planning. If time allows, effort should be made to consult with one's partner, family, oncologist and reproductive endocrinologist so as to make an informed decision about fertility preservation prior to undergoing cancer treatment.

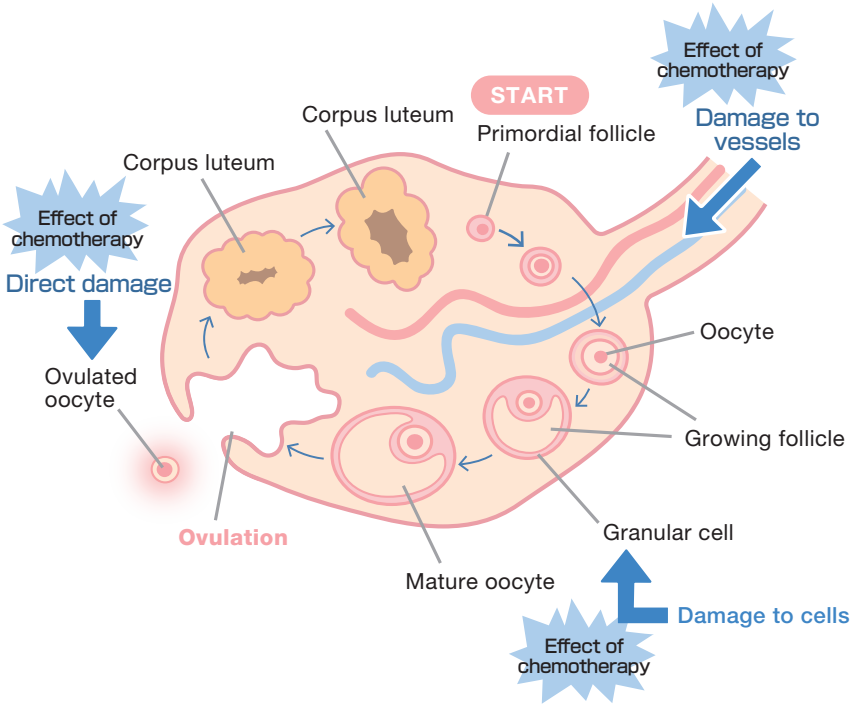
When should I start fertility preservation treatment?

You should first discuss your fertility preservation options with your oncologist to understand both the merits and disadvantages of all preservation options. As preservation treatments must be performed before cancer treatment can proceed, it is sometimes necessary to adjust the treatment schedule if possible. Complications such as bleeding or infection may occur with transvaginal oocyte retrieval and ovarian sectioning.



How cancer treatment affects ovarian functions

The figure below shows how the normal follicular development cycle can be damaged by chemotherapy.



There are many oocytes called "primordial follicles" in the ovary. Reduction in the number of primordial follicles due to cancer treatment is considered to be a cause of infertility. The effects of anticancer drug treatment on ovarian function vary among the individuals, as well as on the type and stage of cancer.

Effect of chemotherapy and radiation therapy

The effect of chemotherapy and radiation therapy on ovarian function varies depending on the type and amount of chemotherapeutic agent administered, and may act directly on the ovary and its functions. After agents are administered, ovarian function is suppressed within two to three months post-initiation, often causing a halt in menstruation. In general, the older the individual, the higher the likelihood of total menstrual cessation. Even if menstruation resumes, ovarian function may not necessarily be restored.

Infertility Risk Associated with Specific Cancer Treatments and Regimens

Risk	Cancer treatment	
High Risk	Cyclophosphamide Ifosfamide Dacarbazin	Cranial irradiation Total body irradiation (TBI) Whole abdominal or pelvic radiation
Intermediate Risk	Cisplatin Carboplatin Doxorubicin Etoposide	Pelvic radiation
Low Risk or No Risk	Actinomycin D Vincristine Methotrexate Fluorouracil Bleomycin	Radioactive iodine
Unknown Risk	Paclitaxel Docetaxel Gemcitabine Irinotecan	

Effect of hormonal therapy

How hormonal therapy affects ovarian function is still unclear. As hormonal agents used in breast cancer and uterine cancer can cause fetal malformations, contraception during treatment is necessary. Hormonal therapy for breast cancer has a long treatment period of 5 to 10 years, so natural pregnancy may be difficult and the risk of delivery will be higher due to aging. In addition, it has

been reported that there is a high possibility that resumption of menstruation is delayed or menopause is stared when hormonal therapy is continued after chemotherapy in the treatment of breast cancer, to compared with treatment without endocrine therapy. It also should be noted that adding hormonal therapy to breast cancer treatment regime can delay menstruation recovery even further or cause early menopause.

Effects of molecular targeted drugs

Although the extent of influence of molecular-targeted drugs on ovarian function is not yet fully known, some of these drugs may affect ovarian function.

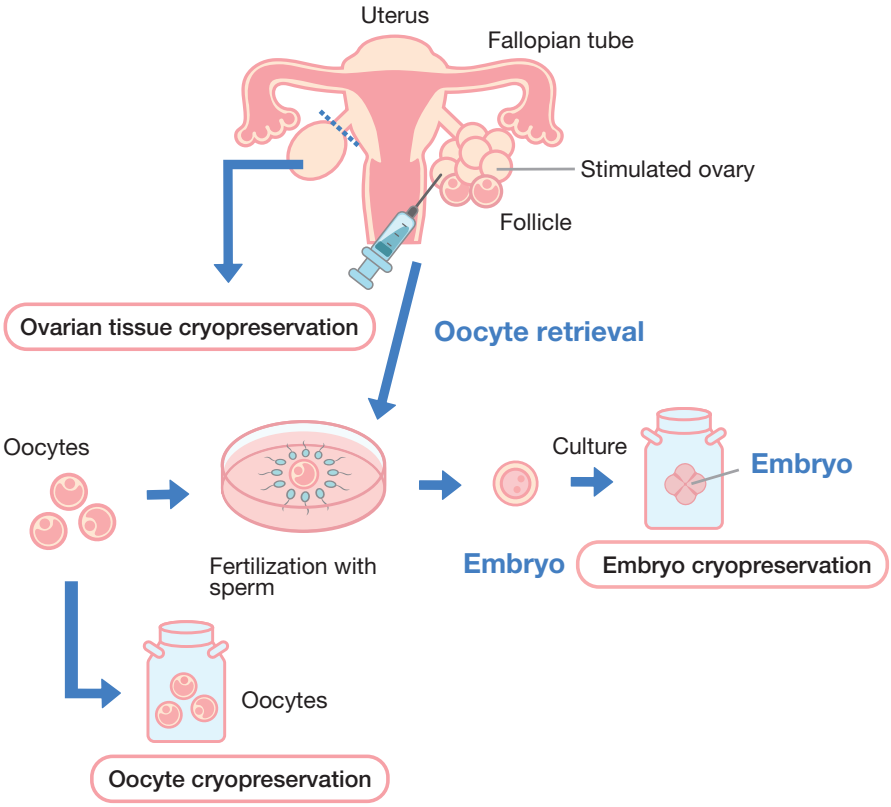
It is difficult to predict whether menstruation will resume after chemotherapy or hormonal therapy. Even if menstruation resumes, this does not ensure that pregnancy is possible. Because individual differences and conditions vary, you should always consult your reproductive endocrinologist about fertility options prior to beginning cancer treatment.

How aging affects egg quality and ovarian function

Reproductive function decreases from ages in the 30s onward, and natural pregnancy becomes difficult from approximately 10 years prior to menopause. This limit is largely due to the risk of abortion, fetal malformation, and other complications that may arise during late pregnancies. By age 40, half of a woman's eggs are chromosomally abnormal, and a few years later that figure rises to over 90%.
In addition to age-related complications, chemotherapy may directly damage the ovaries. This is a possibility that should also be taken into consideration.

Fertility preservation options

Two fertility preservation options available to you are oocyte/embryo cryopreservation and ovarian tissue cryopreservation.



Fertility preservation options

	Oocyte cryopreservation	Embryo cryopreservation	Ovarian tissue cryopreservation
Advantages	• No requirement of partner	• Established method • Pregnancy rate are higher	• No time delay • No requirement of partner
Disadvantages	• Lower pregnancy rate than embryo cryopreservation • Requires ovarian stimulation • Risk of gonadal hormone elevation	• Requires partner • Requires ovarian stimulation • Risk of gonadal hormone elevation	• Experimental method • Surgical procedure • Risk of re-seeding cancer cells

	Oocyte cryopreservation	Embryo cryopreservation	Ovarian tissue cryopreservation
Period	2 ～ 6 weeks	2 ～ 6 weeks	1 ～ 3 weeks
Partner	Not necessary	Necessary	Not necessary
Pregnancy success rate	Lower pregnancy rate than embryo cryopreservation	Higher	Experimental
Birth cases	Established but less case than embryo cryopreservation	Established	Over 60 cases
			• Surgical procedure • Risk of re-seeding cancer cells

Ovarian stimulation is necessary to collect a sufficient number of eggs for egg/embryo cryopreservation. While there are various methods of ovarian stimulation, nearly all require that stimulation proceed for roughly 1 to 2 weeks. In addition, with the increasing level of estrogen, and depending on the type of cancer you will be treated for, ovarian stimulation may not be recommended.

Pregnancy after cancer treatment

How transplantation proceeds after cancer treatment

Egg Cryopreservation

Before transplantation, frozen eggs are thawed and then microscopically inseminated with the partner's sperm. Microscopic fertilization is necessary as frozen eggs cannot be fertilized naturally. Once fertilization is confirmed, the embryo is transplanted into the patient's uterus.

Embryo Cryopreservation

The frozen embryo is thawed and transplanted it into the uterus.

Ovarian Tissue Cryopreservation

The frozen ovarian tissue is thawed and transplanted it to the inside of the body (such as the ovary on the side not collected) by surgery. If the recovery of the function of the transplanted ovary is confirmed, natural pregnancy or in vitro fertilization can be tried. However this is an experimental surgical procedure, and only limited facilities can offer this procedure in Japan.

When should I receive reproductive medical care after cancer treatment?

- If you would like to try to become pregnant after cancer treatment, you should consult with your oncologist because the scheduling needs to be coordinated with your cancer treatment plan.
- Since the safety of pregnancy/childbirth using reproductive medicine after cancer treatment is still unclear, you would need to consult with your oncologist in advance.

Family planning after cancer treatment

- Ask your doctor about fertility before cancer treatment.
- Natural pregnancy is possible in some cases.
- Since spontaneous pregnancy may be difficult depending on your pretreatment and cancer therapy, ask reproductive endocrinologist about fertility preservation options.
- It may be difficult to have a child in a situation of illness, health condition after treatment, original infertility and so on.
- Even if you do not receive fertility preservation treatment before cancer treatment, fertility after treatment may be possible, so consult your reproductive medical doctor.
- You may have to think about a lot of things and feel burdened. Please do not hold it alone and talk to the medical staff about your feelings.

For patients who undergo fertility preservation treatment

- Please carry out the renewal procedure for frozen-preserved embryo/ oocytes as necessary.
- If you wish to conceive using frozen embryos or oocytes after cancer treatment, please consult with your reproductive endocrinologist.
- Please be aware that it may be difficult to transfer frozen-preserved embryos or oocytes to other medical institutions. Also, if you receive fertility treatment using cryopreserved embryo (fertilized egg) , it can only be with the partner at the time of preservation.
- Using fertility preservation before cancer treatment does not guarantee future pregnancy.

For Partner

- It is important that the partner is in good general health.
- In the case of death or divorce preserved embryos cannot be used.
- Frozen embryos, eggs, or sperm can not be used without the consent of the patient.

Flow chart for fertility preservation options

1. Ask your oncologist, nurses, pharmacists, medical social worker or psychologist about fertility preservation.

2. Ask your oncologist about whether your reproductive function will be affected by your cancer treatment.

3. Select a reproductive endocrinologist.

4. Request a letter of introduction from the oncologist to the reproductive endocrinologist.

5. The reproductive endocrinologist will explain your current fertility and preservation options. (Your health insurance may not cover this fee. Please contact your reproductive medical institution for details.)

6. **If you opt for fertility preservation**
   You will undergo treatment at a reproductive medical institution.
   If you select not to pursue fertility preservation prior to treatment
   You may contact a reproductive endocrinologist after cancer treatment as needed.

7. After consulting about your fertility, you are ready to start your cancer treatment at your hospital.

How to find reproductive medical institutions

Consult your oncologist first. Several resources are available to you.

- **Japan Society for Fertility Preservation（JSFP）**
  日本・がん生殖医療学会　https://www.j-sfp.org/
- **Information Center for Cancer Patients**
  がん・情報サービス　https://ganjoho.jp/public/index.html
- **Oncofertility for Children and Adolescents**
  小児・若年がんと妊娠　https://www.j-sfp.org/ped/index.html

Costs for fertility preservation

Reproductive medicine is not covered by insurance.
Be advised that you will receive this treatment at your own expense.

Standard costs

- Counseling : First visit　Thousands to 10000 yen
- Oocytes cryopreservation : 200,000 yen to 400,000 yen
- Embryo cryopreservation : 300,000 yen to 500,000 yen
- Ovarian tissue cryopreservation 600,000 yen to 800,000 yen
- Sperm cryopreservation : 50,000 yen
  (If testicular extraction is required 400,000 yen to 500,000 yen)
- Annual storage fee for cryopreservation : 200,00 yen to 600,00 yen
- Micro insemination using cryopreserved sperm : 350,000yen to 400,000 yen

— Infertility treatment is covered by insurance from April 2022 in Japan, while fertility preservation for cancer patients is not covered by insurance.

— The Ministry of Health, Labour and Welfare launched the "Project to promote Fertility Preservation for Children and AYA Cancer Patients" from April 1, 2021. You can receive some subsidies for the fertility preservation treatment. For more information, please contact your local government.

Calendar

Annotate as you please

- **Cancer treatment**

- **Scheduled date of cancer treatment start Day/Month/Year**

Day _____ **Month** _____ **Year** _____

- **First reproductive medical examination date Day/Month/Year**

Day _____ **Month** _____ **Year** _____

- **Schedule of fertility preservation treatment**

- **Your fertility preservation option**

Embryo freezing / Oocyte freezing / Sperm freezing / Ovarian tissue cryopreservation / others

Data fertility preservation was performed

Day _____ **Month** _____ **Year** _____

Presence / absence of cryopreservation

Update frequency of cryopreservation

Questions you should ask your oncologist

Reproduction medical institutes will need the following information from your oncologist.

- **Primary site of cancer**
- **Stage, prognosis**
- **Scheduled start date of cancer treatment**
- **Treatment (Chemotherapy, Operation, Radiation therapy)**
- **Urgency of cancer treatment (Time needed for fertility preservation)**
- **The risk of infertility by cancer treatment**
- **Contact information of oncologist for reproductive endocrinologist.**

Please review the six checkpoints on page 2 after you talk with your reproductive endocrinologist to check whether you now have full information to make your own decision.

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Working Panel Tasked with Compiling Evidence Regarding the Fertility of Long-Term Survivors of Cancer during Childhood or Adolescence and with Developing a Reproductive Medicine Network (Organizer: Yoko Miyoshi)

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